(Table A24.—Experiments concerning the atherogenic effect of nicotine administration (cont.))

Author, year, country, reference	Number and type of animal	Procedure			Results
		Nicotine	*Diet*	*Vitamin D*	
Hass et al., 1956, U.S.A. (*80*).	Male rabbits	I. (8) Control II. (7) Control III. (14) Nicotine IV. (15) Nicotine V. (9) Control VI. (14) Nicotine (Sacrificed at various times) Control—no treatment. Nicotine—subcutaneous injections in oil—increasing amounts 2 times per week. Vitamin D—subcutaneous injections up to 6–8 x 10^6 IU. Cholesterol—250–500 mg. cholesterol added per 100 g. diet.	Control Cholesterol Control Cholesterol Cholesterol Cholesterol	Control Control Control Control Vitamin D Vitamin D	I. Infrequent medial calcific disease without lipid localization. II. No medial calcific disease but frequent intimal atheroma formation. III. Rare calcific medial degeneration; no intimal atheromatous disease. IV. The largest number of atheromatous lesions. V. No medial calcific disease. VI. Consistent medial calcific disease.
Choi, 1967, Korea (*48*).	Albino rabbits	I. Nicotine 1–5 mg./kg./day intraperitoneally. Cholesterol 1 g./day (in varying combinations with controls). II. Nicotine alone. III. Cholesterol alone. (Sacrificed at 60 days)			I. Increasing nicotine dosages were associated with decreased atheroma formation (findings not statistically significant). II. Nicotine alone produced no atheroma formation but was associated with the presence of aortic medial calcification and endothelial hyperplasia. III. Cholesterol alone was associated with a definite increase in atheroma formation.
Stefanovich et al., 1969, U.S.A. (*178*).	Female albino rabbits.	I. (10) Diet supplemented with 2.0 percent cholesterol. Nicotine intramuscularly 2.78 mg./kg./day, 5/7 days. II. (10) Cholesterol only. III. (10) Nicotine only. IV. (10) Control.	*Percent of aortic surface involved with atherosclerosis* I. 9.4 II. 6.7 III. 0.1 IV. ..		In both stock and cholesterol-fed animals, nicotine was also noted to increase aortic triglyceride content and to decrease aortic free cholesterol content.

(*147*) Page, I. H., Lewis, L. A., Moinuddin, M. Effect of cigarette smoking on serum cholesterol and lipoprotein concentrations. Journal of the American Medical Association 171(11): 1500–1502, November 14, 1959.

(*104*) Kershbaum, A., Bellet, S., Dickstein, E. R., Feinberg, L. J. Effect of cigarette smoking and nicotine on serum free fatty acids. Based on a study in the human subject and the experimental animal. Circulation Research 9(3): 631–635, May 1961.

(*103*) Kershbaum, A., Bellet, S., Caplan, R. F., Feinberg, L. J. Effect of cigarette smoking on free fatty acids in patients with healed myocardial infarction. American Journal of Cardiology 10(2): 204–208, August 1962.

ATLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids*
(Human Studies)

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Page et al., 1959, U.S.A. (*147*).	13 male and 7 female laboratory workers 17–51 years of age.	2 nonfiltered cigarettes in 10 minutes and blood levels measured over 30-minute period.		No change.		*Serum lipoproteins* No change (10 subjects).	
Kershbaum et al., 1961, U.S.A. (*104*).	31 male patients or staff 16–72 years of age. 7 normals. 7 CHD. 17 other medical diagnoses.	I. 17 subjects smoked 2 non-filter cigarettes in 10 minutes. II. 9 controls. III. 5 subjects smoked 6 cigarettes in 40 minutes.	*Mean rise* I. 351 μEq./L. II. 9.8 μEq./L. III. 272–2,304 μEq./L.	No change.	No change.		The authors consider the increase among controls to be due to fasting.
Kershbaum et al., 1962, U.S.A. (*103*).	I. 17 male patients with healed myocardial infarctions. II. 16 non-CHD patients. III. 10 normals. IV. 13 normals.	I., II., III., 2 non-filter cigarettes in 10 minutes. IV. No smoking.	*Mean rise* I. 865 μEq./L. II. 320 μEq./L. III. 232 μEq./L. IV. 20 μEq./L.				No difference found between results following inhalation or noninhalation. Statistically significant difference found between increases in Groups II and III and Group I.

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TABLE A25.—*Experiments concerning the effect of smoking and nicotine upon blood lipids (cont.)*

(Human Studies)

[SM = Smokers NS = Nonsmokers]

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Kershbaum et al., 1963, U.S.A. (*109*).	11 normal patients.	9 standard cigarettes in 3 hours. Samples at 10, 20, and 40 minutes of smoking period.	Definite increase at start of smoking period.			8 patients with trimethaphan camphorsulfonate (Arfonad) pretreatment and 8 formerly adrenalectomized patients showed either minimal or no elevation.	Both free and total urinary catecholamines increased with smoking and the author considers them as mediators of the FFA increase.
Knuttinen and Rajasalmi, 1963, Finland (*120*).	40 healthy moderate smokers 19–20 years of age.	Fed at fat meal and then 20 were allowed to smoke cigarettes of known-nicotine content over 6 hour period (approximately 23 cigarettes consumed).	NS—definite increase at 6 hours. SM—definite increase at 6 hours.	No change in either group.	NS—definite increase at 2 hours. SM—slight increase at 2 hours.		
Kedra et al., 1965, Poland (*101*).	37 male and 5 female medical students 22–23 years of age.	3 cigarettes smoked in rapid succession and samples taken at 10 and 30 minutes.	No change.	No change.		Beta-lipoproteins definite increase.	

(*120*) KONTTINEN, A., RAJASALMI, M. Effect of heavy cigarette smoking on post-prandial triglycerides, free fatty acids, and cholesterol. British Medical Journal 1(5334): 850–852, March 30, 1963.

(*101*) KEDRA, M., POLESZAK, J., PITERA, A. Wplyw palenia tytoniu na poziom tluszczowcow krwi. (Influence of tobacco smoking on the blood lipid levels.) Polski Tygodnik Lekarski 20(39): 1452–1454, September 27, 1965.

(*205*) WENZEL, D. G. BECKLOFF, G. L. The effect of nicotine on experimental hypercholesterolemia in the rabbit. Journal of the American Pharmaceutical Association; Scientific Edition 47(5): 338–343. May 1958

(*107*) KERSHBAUM, A., BELLET, S., KHORSANDIAN, R. Elevation of serum cholesterol after administration of nicotine. American Heart Journal 69(2): 206–210, February 1965.

TABLE A25a.—*Experiments concerning the effect of smoking and nicotine upon blood lipids*

(Animal Studies)

ANIMAL AND IN VITRO STUDIES

Author, year, country, reference	Number and type of population	Smoking procedure	Plasma free fatty acids	Serum cholesterol	Serum triglycerides	Other	Comments
Wenzel and Beckloff, 1958, U.S.A. (*205*).	48 male New Zealand white rabbits.	I. Untreated control—12 subjects. II. Regular diet plus 0.1 percent cholesterol—12 subjects. III. Regular diet plus 2.28 mg./kg./day nicotine in water—12 subjects. IV. Diet plus— (a) 0.1 percent cholesterol (b) 2.28 mg./kg./day nicotine in water—12 subjects.				Group II and IV showed an immediate increase in plasma cholesterol and phospholipids with a level with a leveling of response at 4 weeks. Group IV showed a further increase at 8–12 week period.	The authors consider an elevated cholesterol/ phospholipid ratio to be a notable indication of atherogenic susceptibility. The concomitant increase in phospholipids with the cholesterol may negate the importance of nicotine-induced hypercholesterolemia as an atherogenic stimulus.
Kershbaum et al., 1961, U.S.A. (*104*).	8 mongrel dogs.	Intravenous infusion of 20 mg./kg. nicotine in 20 minutes.	Definite increase in 13/15 observations.				
Kershbaum et al., 1965, U.S.A. (*107*).	20 adult mongrel dogs.	I. 9 received IM nicotine daily for 6 weeks; up to 1 mg./kg. II. 5 placebo injection. III. 6 control.	I. Significant increase in 8/9 dogs. II. No change. III. No change.		No change in any group.		

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TABLE A25a.—*Experiments concerning the effect of smoking and nicotine upon blood lipids* (cont.)

(Animal Studies)

ANIMAL AND IN VITRO STUDIES

Author, year, country, reference	Number and type of population	Smoking procedure	Serum triglycerides	Plasma free fatty acids	Serum cholesterol	Other	Comments
Kershbaum et al., 1966, U.S.A. (*103*).	28 adult mongrel dogs.	Intravenous infusion of nicotine.		No change.			The authors report on the results of the use of nethalide (a Beta-adrenergic blocker), phenoxybenzamine, and chlorpromazine to block the FFA response to nicotine. Only nethalide was successful and this constitutes an indication that nicotine stimulates beta-adrenergic receptors to release catecholamines which, in turn, stimulate the release of FFA.
Kershbaum et al., 1967, U.S.A. (*110*).	Sprague-Dawley rat fat-pad tissue.	Nicotine perfusion.					Although nicotine perfusion was not associated with FFA release from fat tissue, epinephrine did produce a significant increase in FFA release. The authors conclude that the sympathetic nervous system mediates the FFA response to nicotine in the intact animal.

(*115*) KJELDSEN, K., DAMGAARD, F. Influence of prolonged carbon monoxide exposure and altitude hypoxia on serum lipids in man. Scandinavian Journal of Clinical and Laboratory Investigation 22 (Supplementum 103): 16–19, 1968.

TABLE A26.—*Experiments concerning the effect of carbon monoxide exposure upon blood lipids*

Author, year, country, reference	Number and type of population	Smoking procedure	Results
Kjeldsen and Damgaard 1968, Denmark (*115*).	8 male students 23–27 years of age.	Five daily one-half hour exposures to 0.5 percent CO for 8–10 days. Overall mean COHb resulting was 12.5 percent.	No significant changes in total fatty acids, phospholipids, or triglycerides. Cholesterol showed a significant increase only during the last 3 days of exposure.
Kjeldsen, 1969, Denmark (*113*).	72 female albino rabbits: I. Regular diet, 24 subjects. II. Regular diet plus 2 percent cholesterol, 24 subjects. III. Regular diet plus 2 percent cholesterol, 24 subjects.	I. 12 control and 12 exposed to gradually increasing CO concentrations (0.015–0.40 percent) over a 4-week period. II. 12 control and 12 exposed to 0.020 percent CO for 35 days. III. 12 control and 12 exposed to to 0.020 percent CO for 7 weeks, then 0.036 percent CO for 3 weeks.	I. Serum cholesterol concentrations rose rapidly and then remained slightly above control values for the 4-week period. II. At 35 days, the serum cholesterol concentration in the exposed group was 2½ times that in the control group. III. Serum cholesterol concentrations among those exposed were significantly higher than those in the control group for 6 weeks of the 10-week period.
Kjeldsen, 1969, Denmark (*113*).	24 castrated male albino rabbits. Regular diet plus 2 percent cholesterol.	12 control and 12 maintained at 10 percent oxygen levels for 6 weeks, then 9 percent for 2 weeks.	Serum cholesterol and triglyceride concentrations rose to significantly higher levels during 3 of the 8 weeks. No changes noted in serum phospholipids.

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TABLE A27.—*Smoking and thrombosis*

Author, year, country, reference	Number and type of population	Experimental conditions[1]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Blackburn et al., 1959, U.S.A. (25).	16 adult schizophrenic patients, 8 university students, all smokers.	12 individuals smoked 2 high-nicotine standard brand cigarettes.									*Plasma styptven time* (−)	
Mustard and Murphy, 1963, U.S.A. (141).	7 white males with either CVD or COPD, all heavy smokers 35–72 years of age.	Compared after periods of abstinence or continuation of smoking.	(−)	(−)	(−)		(−)	(−)	(+) decrease	(+) increase	*Platelet clumping time* (±)	
Amorus and Mink, 1964, U.S.A. (4).	20 healthy male non-smoking medical students <20 years of age.	Deep inhalation of one nonfiltered cigarette.	(−)		(−)	(−)	(±) increase	(−)			Thromboplastin generation time (−)	2 students became ill. Results reflect data on 18.
Ashby et al., 1965, Ireland (5).	27 male medical students and hospital staff members.	13 controls measured at 2 separate times 14 subjects measured before and after smoking 2 cigarettes in 20 minutes.					(+) increase					Increase of subjects greater than that of controls at $p<0.01$.

TABLE A27.—*Smoking and thrombosis (cont.)*

Author, year, country, reference	Number and type of population	Experimental conditions[1]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Bagai and Joshi, 1965, India (171).	11 observations on male smokers all regular tobacco users.	Smoked 2 cigarettes or 2 biris or chewed 1 betel nut quid in 20 minutes.	(−)	(−)		(−)	(+) increase				*Fibrinolysis* (+) decrease	biri—tobacco wrapped in tobacco leaf.
Engelberg, 1966, U.S.A. (58).	40 male and 20 female hospital patients, all smokers 17–68 years of age.	2 cigarettes in 20 minutes.									*Chandler (in vitro) thrombosis time* + decrease	
Kedra and Kozelka, 1965, Poland (100).	39 male and 11 female smokers and 24 male and 26 female nonsmokers 18–35 years of age.	6 cigarettes in 1 hour.	(±) decrease	(−)		(+) decrease					Thrombin time (±) decrease	
Murchison and Fyfe, 1966, Scotland (138).	8 males and 4 female patients with various diseases, all heavy smokers 37–67 years of age.	2 cigarettes in 15 minutes. 2[1] or unfil. cigarettes.					(+)	(+) increase				[1] Smoking both filt and unfilt cigarettes caused a rise in platelet adhesiveness which the authors correlated with rise in plasma non-esterified fatty acids.

(25) BLACKBURN, H., JR., ORSIA, E., HARTEL G., PUNSAR, S. Tobacco smoking and blood coagulation: Acute effect on plasma Stypven time. American Journal of the Medical Sciences 238: 446–451, October 1959.

(141) MUSTARD, J. F., MURPHY, E. A. Effect of smoking on blood coagulation and platelet survival in man. British Medical Journal 1(5334): 846–849, March 30, 1963.

(4) AMERUS, J. L., MINK, I. B. Effect of cigarette smoking on blood coagulation. Clinical Pharmacology and Therapeutics 5(4): 428–431, 1964.

(5) ASHBY, P., DALBY, A. M., MILLAR, J. H. D. Smoking and platelet stickiness. Lancet 2: 158–159, July 24, 1965.

(171) SOCANI, R. K., JOSHI, K. C. Effect of cigarette and biri smoking and tobacco chewing on blood coagulation and fibrinolytic activity. Indian Heart Journal 17: 238–242, July 1965.

(58) ENGELBERG, H. Cigarette smoking and the *in vitro* thrombosis of human blood. Journal of the American Medical Association 193(12): 1033–1035, September 20, 1965.

(100) KEDRA, M., KOKIELKO, A. Tobacco smoking and blood clotting. Bulletin of Polish Medical Science and History 8: 145–148, October 1965.

(138) MURCHISON, L. E., FYFE, T. Effects of cigarette smoking on serum-lipids, blood-glucose, and platelet adhesiveness. Lancet 2(7456): 122–124, July 23, 1966.

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TABLE A29.—*Smoking and thrombosis (cont.)*

Author, year, country, reference	Number and type of population	Experimental conditions[1]	Whole blood clotting time	Prothrombin time	Partial thromboplastin time	Recalcified plasma clotting time	Platelet adhesiveness	Platelet count	Platelet survival	Platelet turnover	Other	Comments
Glynn et al., 1966, Canada (71).	88 male and 17 female smokers and 8 male and 31 female nonsmokers 17–74 years of age.	3 cigarettes in 30 minutes.					(–)				*Platelet serotonin* (–) *Platelet adenosine nucleotide* (–)	Smokers found to have a greater tendency for platelet aggregation than nonsmokers.
Engelberg and Futterman, 1967, U.S.A. (59).	84 male and 63 female patients and medical house staff.	1 cigarette in 6 minutes.									*Thrombus formation time* (+) decrease	No relation found with increase in free fatty acids.
Murphy, 1968, U.S.A. (148).	Literature review with summary of data and conclusions.						(±) Increase	(±) Increase	(+) decrease		*Platelet adherence to vascular endothelium* (+) increase *Fibrinolysis* –(±) decrease *Thrombus formation time* (+) decrease	

Symbols:
– = No effect.
± = Questionable effect.
+ = Definite effect.
[1] Results, unless otherwise stated, concern specific coagulation test as measured before and after smoking procedure noted.

TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system*

Author, year country, reference	
Meyer and Maddock, 1940, U.S.A. (124).	20 subjects (including heavy smokers) were studied for the effects of the following procedures on skin temperature: the inhalation of a lit cigarette, inhalation through an empty paper tube, or the administration of 1 mg. nicotine intravenously. All subjects responded with decreased cutaneous temperature following the smoking and nicotine procedures. No changes were noted following sham smoking.
Mailman and Shulman, 1948, U.S.A. (118).	A number of experimental groups, each consisting of 5–11 persons, were studied for the effects of deep breathing and cigarette smoking on skin temperature and digit or limb plethysmography. The authors concluded that deep breathing alone could account for the changes in temperature and blood flow noted upon smoking and noted that denicotinized cigarettes evoked the same or greater vasoconstriction as that noted following the smoking of a standard cigarette.
Shepherd, 1951, Ireland (173).	10 young male smokers were studied with plethysmography before and after the normal and rapid inhalation of a standard cigarette. The author noted that rapid inhalation was associated with a prolonged decrease in extremity blood flow while a more natural rate of inhalation was followed by a momentary decrease in flow. The author considered the former reaction to represent the pharmacologic effect of the smoke and the latter to represent the physiologic response to deep breathing, as the natural inhalation of an calit cigarette produced the same transient decrease in flow as did the natural inhalation of the lit cigarette.
Friedell, 1953, U.S.A. (70).	52 male and 45 female young smokers and nonsmokers were studied for the effects of smoking on hand blood volume as measured by the use of radioactive iodinated albumin. The inhalation of unfiltered cigarettes was associated with an average decrease in hand blood volume of 19 percent in men and 33 percent in women; while filtered cigarettes showed respective decreases of 11 percent and 21 percent.
Strömblad, 1959, Sweden (181).	11 male and female subjects (smokers and nonsmokers) were studied for the effect of the intra-arterial administration of nicotine (brachial artery) on blood flow to the hand as measured by venous occlusion plethysmography. Increasing doses of nicotine were associated with increasing numbers of individuals manifesting vasoconstriction. The vasoconstrictive effects of nicotine were abolished by the prior administration of either hexamethonium or pentolinium.
Barnett and Boake 1960 Australia (13).	8 male patients with intermittent claudication (7 were heavy smokers) were studied for the effect of smoking on blood flow to the leg as measured by venous occlusion plethysmography. Smoking an unfiltered cigarette was found not to produce any consistent changes in blood flow to the calf or foot of the affected leg.
Freund and Ward, 1960, U.S.A. (68).	15 male prison inmates (less than 35 years of age) and 14 male patients with peripheral vascular disease (approximately 65 years of age) were studied for the effect of smoking on digital circulation as measured by skin temperature, plethysmography, and radioisotope clearance from the skin. Smoking was found to adversely affect the first and third measures in a significant manner (while plethysmographic values were variable) only in the healthy prisoners and not of all in the patient group.
Roth and Schick, 1960, U.S.A. (161).	100 normal individuals underwent 425 experimental procedures concerning the effect of smoking on the peripheral circulation. Smoking was found to be associated with a decrease in extremity skin temperature.

(71) GLYNN, M. F., MUSTARD, J. F., BUCHANAN, M. R., MURPHY, E. A. Cigarette smoking and platelet aggregation. Canadian Medical Association Journal 95(11): 549–553, September 10, 1966.

(59) ENGELBERG, H., FUTTERMAN, M. Cigarette smoking and thrombotic coagulation of human blood. Arenives of Environmental Health 14(2): 256–270, February 1967.

(124) MOYER, C. A., MADDOCK, W. G. Peripheral vasospasm from tobacco. A.M.A. Archives of Surgery 49(2): 277–285, February 1940.

(118) MULINOS, M. G., SHULMAN, I. The effects of cigarette smoking and deep breathing on the peripheral vascular system. Studied by five methods. American Journal of the Medical Sciences 199(5): 708–720, May 1940.

(173) SHEPHERD, J. T. Effect of cigarette-smoking on blood flow through the hand. British Medical Journal 2: 1007–1010, October 27, 1951.

(70) FRIEDELL, M. T. Effect of cigarette smoke on the peripheral vascular system. Radioactive iodinated albumin used as indicator of volumetric change. Journal of the American Medical Association 152(10): 897–900, July 4, 1953.

(13) BARNETT, A. J., BOAKE, W. C. Cigarette smoking and occlusive arterial disease of the legs. Medical Journal of Australia 1: 240–242, February 13, 1960.

(161) ROTH, G. M., SCHICK, R. M. The effects of smoking on the peripheral circulation. Diseases of the Chest 37(2): 203–210, February 1960.

71 124

TABLE A30.—*Experiments concerning the effect of nicotine and smoking upon the peripheral vascular system* (cont.)

Author, year, country, reference	
Bonnheim et al., 1960, U.S.A. (16).	6 males (18–31 years of age) were studied for the effect of intravenous nicotine on extremity temperature and blood flow. Intravenous nicotine was found to evoke a decrease in skin temperature while increasing muscle blood flow. The former effect began sooner and lasted longer than the latter.
Ramsey and Roth, 1960, U.S.A. (143).	30 healthy individuals (19–59 years of age) were studied for the effect of smoking two cigarettes on extremity pulse volumes and skin temperatures. Smoking was found to be associated with a 2–4 percent decrease in skin temperature and a 45–50 percent decrease in blood pulse volumes in segments of the finger, calf, and toe.

(162) ROTTENSTEIN, H., PRINCE, G., RUSS, E., FELDER, D., MONTGOMERY, H. Influence of nicotine on the blood flow of resting skeletal muscle and of the digits in normal subjects. Annals of the New York Academy of Sciences 90(1): 102–113, September 27, 1960.

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1972 Page 460

The Health Consequences of Smoking

A Report of the Surgeon General: 1972

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Health Services and Mental Health Administration

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Contents

	Page
Coronary Heart Disease	
Introduction	13
Epidemiological Studies	14
Interaction of Smoking and Other Risk Factors	16
Autopsy Studies	19
Experimental Studies	21
Nicotine and Cigarette Smoke	21
Carbon Monoxide	21
Smoking and Thrombosis	23
Cholesterol Content of Tobacco and Tobacco Smoke	24
Cor Pulmonale (Pulmonary Heart Disease)	24
Cerebrovascular Disease	24
Peripheral Vascular Disease	25
Oral Contraceptives, Thrombophlebitis, and Smoking	26
Highlights of Current Cardiovascular Information	27
References	27

LIST OF TABLES

Table 1.—Incidence (1963–1970) of heart infarct in relation to tobacco consumption in "The Men Born in 1913," Göteborg, Sweden	15
Table 2.—Cigarette smoking at entry and subsequent 20-year CHD incidence among Minnesota men	15
Table 3.—Human autopsy study. Comparison of the thickness of myocardial arteriole walls in smokers and nonsmokers	19
Table 4.—Average values of carboxyhemoglobin and serum cholesterol in Danish smokers and nonsmokers in control group and group of patients with arteriosclerotic cardiovascular disease	23

LIST OF FIGURES

	Page
autopsy study. Comparison of the thickdial arteriole walls in 32 smoking dogs days and 8 nonsmoking dogs	20

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INTRODUCTION

In the United States more people die from coronary heart disease (CHD) than from any other disease; furthermore, CHD is the single most important cause of excess death among cigarette smokers (54, 57). The 1971 report, "The Health Consequences of Smoking" (56), outlined the growing magnitude of this problem and summarized the relationship between smoking and coronary heart disease as follows:

1. Data from numerous prospective and retrospective studies confirm the judgment that cigarette smoking is a significant risk factor contributing to the development of coronary heart disease including fatal CHD and its most severe expression, sudden and unexpected death. The risk of CHD incurred by smokers of pipes and cigars is appreciably less than that by cigarette smokers.
2. Analysis of other factors associated with CHD (high serum cholesterol, high blood pressure, and physical inactivity) shows that cigarette smoking operates independently of these other factors and can act jointly with certain of them to increase the risk of CHD appreciably.
3. There is evidence that cigarette smoking may accelerate the pathophysiological changes of pre-existing coronary heart disease and therefore contributes to sudden death from CHD.
4. Autopsy studies suggest that cigarette smoking is associated with a significant increase in atherosclerosis of the aorta and coronary arteries.
5. The cessation of smoking is associated with a decreased risk of death from CHD.
6. Experimental studies in animals and humans suggest that cigarette smoking may contribute to the development of CHD and/or its manifestations by one or more of the following mechanisms:
   a. Cigarette smoking, by contributing to the release of catecholamines, causes increased myocardial wall tension, contraction velocity, and heart rate, and thereby increases the work of the heart and the myocardial demand for oxygen and other nutrients.
   b. Among individuals with coronary atherosclerosis, cigarette smoking appears to create an imbalance between the increased needs of the myocardium and an insufficient increase in coronary blood flow and oxygenation.
   c. Carboxyhemoglobin, formed from the inhaled carbon monoxide, diminishes the availability of oxygen to the myocardium and may also contribute to the development of atherosclerosis.
   d. The impairment of pulmonary function caused by cigarette smoking may contribute to arterial hypoxemia, thus reducing the amount of oxygen available to the myocardium.
   e. Cigarette smoking may cause an increase in platelet adhesiveness which might contribute to acute thrombus formation.

Recent epidemiological, pathological, and experimental studies add to the understanding of the relationship between smoking and CHD. These studies point to cigarette smoking as one of the major risk factors leading to CHD and help clarify some of the biomechanisms through which this occurs.

(54) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: A Public Health Service Review: 1967. Washington, U. S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1967. 199 pp.

(57) U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1103, 1964. 387 pp.

(56) U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking: A Report of the Surgeon General: 1971. Washington, U.S. Department of Health, Education, and Welfare, DHEW Publication No. (HSM) 71-7513, 1971. 458 pp.

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Acceptance of Morbidity Statistics. In 1971, Sterling published an article in the Journal of the American Statistical Association (66: 251-257), analyzing the statistics used in the earlier documents. The article is reproduced in its entirety.

A Review of the Claim that Excess Morbidity and Disability Can Be Ascribed to Smoking

THEODOR D. STERLING*

This article analyzes an HEW report on smoking and morbidity based on a study suffering from two major flaws. First, the data actually presented in the report may not warrant the conclusion that cigarette smoking leads to increases in disease and disabilities (female smokers, by and large, report fewer diseases than do female non-smokers, and moderate smokers, comprising over 72% of the smoking population for males and over 88% for females, report the fewest number of diseases and have the lowest prevalence rates for both men and women); second, inadequate attention has been paid to the potential influence of various aspects of the survey method on these findings. There appears to be several obvious sources of error for which adjustments were not made.

1. INTRODUCTION

In 1967 the U. S. Department of Health, Education, and Welfare published a report entitled *Cigarette Smoking and Health Characteristics* which offers

> . . . statistics . . . on selected health characteristics and cigarette smoking habits of the civilian, noninstitutional population 17 years and over in the United States during the period July 1964–June 1965 [10, title page].

The report is careful *not* to claim that it establishes a relationship between smoking and chronic and acute illnesses and disabilities. However, it has become the basis for a number of claims that smoking causes a large variety of illnesses and disabilities. These claims are summarized in an official report by HEW which makes specific claims about the total days Americans are supposed to have lost from work or spent at home "because cigarette smokers have higher disability rates than non-smokers" [22]. These figures are large—77 million days lost from work, 88 million days spent in bed, 396 million days of restricted activity. While none of these figures even appear in the original study (they are estimates said to be based on figures contained in that study although the estimating procedures are nowhere published), the same figures are also used widely and continuously in pamphlets circulated by the National Clearinghouse for Smoking and Health and are repeated in a recent information publication prepared by a private contractor [5]. Yet, the data provided by the National Center are extremely ambiguous. (With clever manipulation, they could be made to support the contention that smoking is even beneficial to health.)

Specifically, the study on cigarette smoking and morbidity suffers from two major flaws:

1. The data actually presented in *Cigarette Smoking and Health Characteristics* may not, in fact, warrant the conclusion that cigarette smoking leads to increases in disease and disabilities:
   a. Female smokers, taken as a group, by and large report fewer diseases and disabilities and their prevalence rates, computed on the basis of these reports, are generally smaller than those for non-smokers.
   b. Moderate smokers (those who consume less than a half or less than a full pack a day) very often report the fewest number of diseases and have the lowest prevalence rates for both men and women. If the conclusions of the report hold, they do so for heavier smokers only who comprise considerably less than half the sample of smokers.
2. Inadequate attention has been paid to the potential influences of various aspects of the survey methods on the findings. Specifically, there appear to be a number of obvious sources of bias and error for which adjustments were not made.

The sampling plan of the National Health Survey follows a multi-stage design which permits a continuous sampling of the civilian population of the United States. The first stage of this design consists of drawing a sample of 357 from about 1,900 geographically-defined Primary Sampling Units into which the United States has been divided. The PSU is a county, a group of contiguous counties, or a standard metropolitan statistical area. Within PSUs, ultimate stage units, called segments, are defined in such a manner that each segment contains an expected 900 households. Each week a sample of about 90 segments is drawn. Household members in the approxi-

* Theodor D. Sterling is professor, Department of Applied Mathematics and Computer Science, Washington University, St. Louis, Mo. This article is based on three studies conducted by the author over a two-year period on the validity of recent claims about the effects of smoking on health. The results of these studies were immediately made available to the National Center for Health Statistics, the National Institutes of Health, the cigarette industry, and other interested and appropriate agencies and individuals. In substance this article is based on the author's testimony on April 29, 1969, to the Interstate and Foreign Commerce Committee of the House of Representatives, Representative Harley O. Staggers, Chairman.

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mate 800 of the households in the segments are interviewed concerning factors related to health. Since it would be impossible to interview each person residing in the household, the information about all residents in a household is obtained from adults over 19 who are present when the interviewer calls. These are usually the women homemakers, elderly or retired persons, or ill or unemployed members of the household. Thus, the information is partially collected by direct interview and partially by "proxies." In some five to ten percent of the sample households no interview is obtained for one or another reason. The problem created by this "missing information" is handled in various ways, but whatever procedure is followed it ultimately contributes as an additional source of variability and potential bias.

2. DO THE DATA ACTUALLY SHOW AN ASSOCIATION BETWEEN SMOKING AND DISEASE AND DISABILITY?

Several studies that demonstrated the effect of smoking on health have been criticized sharply because of their methods of obtaining data and of analyzing them. The attitude of these critical evaluations was that since the method of investigation was seriously impaired, the purported findings of the study did not need specific refutation. However, such an assumption may be unfounded, and, indeed, may be a disservice. These attempted refutations gained no strength from the fact that they were advanced by notable statisticians; the truth is that neither to the average physician nor to the man in the street does the name of Berkson or of Sir Ronald Fisher mean any more than Tom, Dick, or Harry. Thus, even when an investigation does not appear to provide a foundation on which to base statistical inference, it is still necessary to examine the data to see whether or not there exists an observed difference between smokers and nonsmokers on which any claims may be based. Besides, such a comparison may prove to be interesting.

2.1 The Female Enigma

Responses by women are based predominantly on self interviews (83 percent) as compared to men, of whom only 40 percent were self interviewed. Since it is known that self interviews are much more accurate than proxy responses [1, 13, 14, 17, 18], a comparison between reported diseases among female smokers and non-smokers would appear to be a much more accurate contrast than the corresponding comparison among males. Yet, the percentage of female non-smokers 17 years of age and over who reported one or more chronic conditions is consistently smaller than that of female smokers. Since there were considerable differences in age distributions between smokers and non-smokers, the data were adjusted to a new base using an indirect method. (We shall discuss the age adjustment method used in a moment and just note now that when this indirect age adjustment is done, the difference between smokers and nonsmokers, especially for males, is often reversed.) However, even if we accept for the moment the age adjustment method, the comparisons between disease rates for chronic conditions between smokers and non-smokers are far from clear. Table 1 shows prevalence rates for females 17 years and over, both unadjusted and adjusted by the indirect method. We see that for heart conditions, hypertension, and hearing impairment the age-adjusted rates remain lower for smokers than for non-smokers. Certainly an inspection of this table, regardless of whether or not we accept the indirect age adjustment method, does not unambiguously lead us to ascribe more disease to smokers.

Table 1. PREVALENCE RATES OF CHRONIC CONDITIONS PER 100 FEMALES 17 YEARS AND OVER IN NHS, BY CIGARETTE SMOKING STATUS

Selected chronic condition	Unadjusted for age[a]			Adjusted for age[b]		
	Total population	Persons who never smoked	Persons who ever smoked	Total population	Persons who never smoked	Persons who ever smoked
Heart condition (excluding rheumatic heart disease)	4.3	5.5	2.6	4.2	4.5	3.9
Arteriosclerotic heart disease, including coronary disease (subcategory of heart conditions)	0.7	0.8	0.6	—[c]	—[c]	—[c]
Hypertension without heart involvement	8.3	10.1	5.8	8.2	8.6	7.4
Chronic bronchitis and/or emphysema	2.0	1.3	3.1	2.0	1.2	3.4
Chronic sinusitis	12.2	11.1	13.9	12.2	11.1	14.0
Peptic ulcer	1.9	1.6	2.5	1.9	1.6	2.6
Arthritis	13.0	15.4	9.7	12.9	12.9	12.8
Hearing impairment	5.7	7.1	3.9	5.6	5.8	5.4
All other chronic conditions	100.8	101.0	98.0	100.1	95.9	107.8
All chronic conditions	149.0	155.9	139.7	147.8	142.2	158.6

[a] *Source:* [16, Table 6, pp. 32–3].
[b] *Source:* [16, Tables 7–17, pp. 34–42].
[c] Not given.

2.2 The Enigma of the Moderate Smoker

Most reports about smoking effects pay close attention to individuals who fall into "heavy" smoking categories. The fact that heavy smokers usually report more diseases than do more moderate smokers is implicitly taken as a function of "dose." However, there are several problems with emphasizing the fate of heavy smokers, of which two deserve special attention:

1. The majority of smokers use cigarettes in moderate amounts [5, 7]. They may report as few or fewer diseases than do non-smokers (as is the case in this report).
2. Heavy smokers are relatively few in number and it is known that they also tend to be heavy drinkers [6], over-eaters (usually inferred from heavier weight of smokers or higher serum cholesterol levels, or both [2, 4, 9, 10, 19]), under-exercisers [21, Table 18], and are perhaps careless about other vices that may detract from their health. It is unclear to what extent these other factors contribute to the observed diseases.

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It is thus not sufficient to report an increase in disease among heavy smokers without clarifying if smoking *in any amount* results in an increase in disease.

What is "moderate" or "excessive" smoking is difficult to define. We have taken a reported smoking rate of one half pack or less as moderate but include also the group reporting a smoking rate of one half to a full pack a day. In so doing, we clearly deal with the majority of smokers, so that observations on them ought to receive proper attention. After all, no fewer than 72.6 percent of the males and 88.5 percent of the female smokers reported that they smoked a pack or less a day presently. Although these percentages decline somewhat if smokers are grouped by heaviest amount smoked daily, those who smoke less than one pack a day make up the overwhelming majority of the smoking population. (Relevant figures are summarized in [16, Table 3, pp. 27–8].)

The report stresses that rates of most diseases and disabilities increase with increases in the number of cigarettes smoked. In a way, this is correct. There is this parallel increase in disease and smoking. The trouble is that, as often as not, non-smokers report disease rates that are greater than those reported by smokers who consume less than a half or full pack a day. Table 2 compares observed prevalence rates and prevalence rates adjusted for peculiarities and difference in age distribution between moderate smokers and non-smokers. Moderate smokers, whether male or female, tend to report less disease than do non-smokers. Similar observations are true for reports of disabling confinements. The number of disease categories for which moderate smokers report a smaller prevalence differ for adjusted and unadjusted prevalence rates. Of those who smoke one half pack or less, males reported fewer diseases in six out of seven disease categories (adjusted or unadjusted) and females reported fewer diseases in six out of eight. For smokers who consume between a half and a full pack a day, males reported fewer diseases in six out of eight disease categories and females in five out of eight (for unadjusted) and three out of eight (for adjusted prevalence rates).

Table 2. ESTIMATED UNADJUSTED AND AGE-ADJUSTED PREVALENCE RATES FOR DIFFERENT CHRONIC CONDITIONS FOR 100 MODERATE- AND NON-SMOKING MALES AND FEMALES[a]

Condition, by sex	Unadjusted			Age-adjusted		
	Never smoked	Half pack or less[b]	Half to full pack[b]	Never smoked	Half pack or less[b]	Half to full pack[b]
Heart condition (excluding chronic rheumatic heart disease)						
Males	4.6	3.2	3.4	4.1	3.8	4.4
Females	5.5	2.0	2.2	4.3	2.6	3.5
Hypertension						
Males	4.4	3.4	3.1	4.1	3.8	3.6
Females	10.1	6.0	5.0	8.6	7.4	6.5
Chronic bronchitis						
Males	1.0	-	2.1	1.0	-	2.3
Females	3.3	1.4	3.4	3.2	1.6	4.0
Chronic sinusitis						
Males	8.2	7.6	10.1	8.3	7.7	10.1
Females	11.1	10.7	13.9	11.1	10.8	14.0
Peptic ulcer						
Males	2.3	2.3	4.6	2.4	3.0	4.6
Females	1.6	1.9	2.4	1.6	2.0	2.5
Arthritis						
Males	7.3	5.5	5.0	6.8	6.6	5.9
Females	15.4	8.7	9.1	12.9	11.1	12.5
Hearing impairment						
Males	8.9	6.9	6.2	8.0	7.0	7.5
Females	7.1	3.2	3.7	5.8	4.2	5.3
11 other chronic conditions						
Males	74.8	62.7	69.8	72.5	65.4	75.0
Females	133.0	78.5	89.4	95.9	85.1	99.5

[a] *Source:* [16, Tables 8–15, pp. 35–42].
[b] By heaviest amount smoked.

Of course, the non-smoker category may include a certain number of persons who do not smoke because of chronic illness. Yet, there is no substantive evidence offered that this is so or that moderate smoking is not prevalent among individuals who are ill from a number of causes. On the other hand, we cannot explain the higher prevalence of morbidity among non-smokers because a certain number of the very ill smokers may have been urged or forced to join the non-smokers. We purposely selected persons who never smoked to compare with moderate smokers. In short, while the peculiarities in the relationship between the amount smoked and the number of diseases reported make it difficult in the extreme to explore and explain these data, it is not easy to see what purpose could be served by hiding this pertinent result by a blanket statement that the increase in disease appears to be related to the amount smoked.

3. WHAT WERE THE POTENTIAL INFLUENCES OF THE SURVEY METHODS ON THE FINDINGS?

The National Center for Health Statistics has been in the forefront of developing and investigating probability sampling methods, attendant survey methodology, and sources of error and ways to adjust for them. For this reason, it is not easy to understand why so many potential sources of bias were simply ignored. This is doubly surprising because the basic methodological investigations that have shown only a small correlation between the incidence of medically-documented disabilities and the estimated number of these same diseases derived from questionnaire interview methods come from two widely-known and well-respected studies sponsored by and published through the NCHS. These detailed studies had shown that proxy responses tend to suffer from errors roughly twice the size of those which result from self respondents [13, 14]. One of these studies is especially relevant because it demonstrated that "psychological" or "sociological" factors have profound effects on the size of errors in responses of proxies, much more so than on responses that came from self respondents [14].

An interview technique which obtains data about a larger population by interviewing those members of a household who are fortuitously present when the interviewer calls was, in fact, recognized during the inception of the National Health Survey as a serious source of error and the budgetary limitations forcing this procedure upon

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the survey properly lamented [11, 12]. Yet, national estimates on the effect of smoking are based on these same data, with the fond hope that errors in them are randomly distributed throughout all categories of information so that estimates of different categories (such as for smokers and non-smokers) are not affected differentially.[1] Given the public nature of debate on smoking and health in the press and on television, there is surely a good possibility that proxy respondents may be affected by opinions and beliefs concerning smoking and, accordingly, color their answers to interviewers. Similar problems exist for such obvious potential sources of bias as employment or non-employment or for other "characteristics" of respondents.

3.1 The Smoking-Proxy Bias

The survey obtained records for 41,745 males. Of these, 29,322 were reported to be smokers. Only 12,440 smoking males reported directly about their disease and disabilities. Of the smoking males for whom information was obtained by proxy, the largest group had information obtained from their spouse. Counting only wives who either smoked or did not at the time of the interview, there were 11,440 such male smokers, comprising approximately 40 percent of the sample of male smokers. It may be reasonable to suppose that among non-smoking informants (mostly wives) there are those who do not smoke because of the belief that smoking could be harmful. By comparing the number of diseases reported for smokers by informants who do smoke and informants who do not smoke, we can isolate to some extent the effect of the belief (that may be held consciously or not) that smoking is harmful in terms of the number of diseases each group reports for their smoking husband.

The 11,440 male smokers were divided into the 5,678 proxies whose wives had never smoked and the 5,562 proxies whose wives smoked at the time of interview. The percentage of smoking males for whom one or more chronic conditions were reported by the wife, the percentage for whom different kinds of chronic conditions were reported, and the average number of chronic conditions reported for each proxy for whom diseases were reported are shown in Table 3. As can be seen, non-smoking wives uniformly reported more disease for their smoking husbands than did the wives who themselves did smoke. But not only were more individuals reported as having disease by non-smoking than by smoking wives, but the number of diseases reported for each husband was also affected by whether or not the wife smoked.

The comparison of the number of diseases reported by smoking and non-smoking informants is of special significance for the category of bronchitis/emphysema. Since smokers often cough, the question may be raised to what extent this cough is perceived by non-smokers as a sign of disease while it may be largely ignored by smokers as a simple response to irritation. Certainly it would be unreasonable to suppose that the wife's failure to smoke causes an increase in the number of instances of husbands with bronchitis and emphysema (or of any other chronic disease).

Table 3. PERCENT OF PROXY SMOKING MALES FOR WHOM CHRONIC CONDITIONS, RESTRICTED ACTIVITY, CONFINEMENT TO BED, AND LOST DAYS OF WORK WERE REPORTED BY SMOKING AND NON-SMOKING WIVES[a]

Condition	Wife does not smoke	Wife smokes
One or more chronic conditions	57.7%	56.0%
Heart disease	3.10	3.00
Hypertension	3.63	3.16
Bronchitis/emphysema	2.10	1.75
Chronic sinusitis	11.10	11.03
Peptic ulcers	4.75	4.72
Prevalence of restricted days because of illness:		
Restricted activity days during last two weeks	7.90	7.49
Days spent in bed during last year	12.48	12.11
Days lost from work during last two weeks	4.61	3.83
Average number of all chronic conditions reported	1.94	1.77
Average number of restricted days because of illness:		
Average restricted activity days during last two weeks	5.65	5.54
Average days spent in bed during last year	24.46	19.16
Average days lost from work during last two weeks	5.80	4.00

[a] From data supplied by the National Center for Health Statistics.

Very much the same picture emerges when we compare the number of restricted activity days, days spent in bed, and days lost from work and the average number of such lost days reported by wives who smoke with the number reported by wives who do not smoke. The percentage of males for whom it is reported that they have lost days is uniformly smaller if the wife reporting these disabilities does smoke than if the wife does not. The same is true for average number of days reported with the exception of work-loss days where smoking wives report more work days lost than nonsmoking wives.

Since the difference in the raw prevalence of reported diseases and disabilities as described in [16] is often no larger and sometimes even smaller than the prevalence in reported disease and disabilities between smoking and non-smoking proxy informants, it is not impossible that the observed difference in prevalence between smokers and non-smokers may have been due to these psychological factors. In any case, it seems a pity that the proper adjustment for this factor was not included in the analysis of the NCHS data.

[1] Personal communication from Mr. Theordore D. Woolsey, the Director of NCHS.

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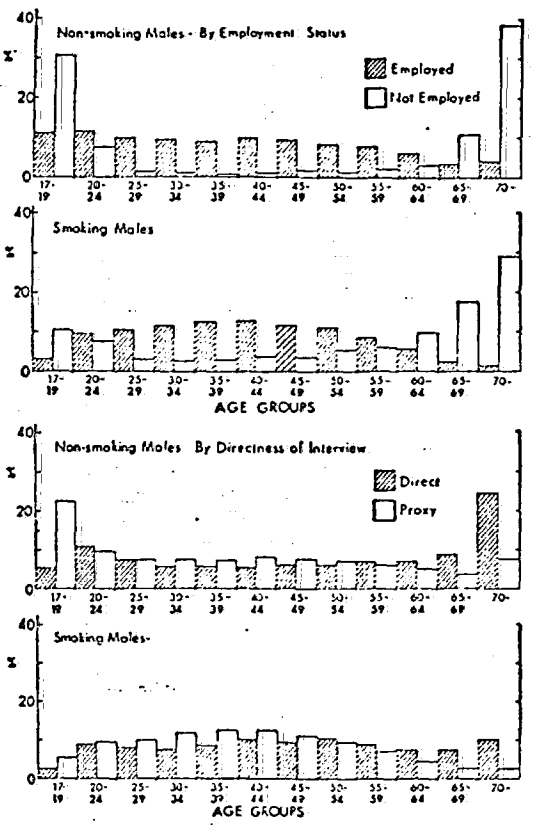
3.2 The Adequacy of Age Adjustment Methods

There are several methods of comparing two sets of rates when large confounding effects may differentially distort them. One of the obvious confounding effects in comparing disease rates is age. Disease rates are obviously related to age, with the highest rates occurring among the very young and the aged. If the age distribution for smokers and non-smokers were similar, then rates of disease among them could be compared directly. However, the age distributions of sampled smokers and non-smokers were quite different. Thus, observed differences in disease rates between smokers and non-smokers may be related to differences in their age distributions rather than to the fact that they differ in smoking habits. The data in the report *Cigarette Smoking and Health Characteristics* were adjusted, therefore, for peculiarities of their age distribution. There are, however, two objections to the analyses in the report.

Adjustments do not go far enough. There are a number of differences between smokers and non-smokers other than age and sex that need to be considered. Observed differences in rates between smokers and non-smokers may be related to differences between the two groups on such factors as employment status, directness of interview, characteristics of proxy informants, and so on. Secondly, the indirect method of age adjustment used in the report is most easily affected by extraneous factors and ought not to have been used.

The figure gives some idea of the differences between male smokers and non-smokers on employment status and directness of interview by age. (The distributions are as markedly different for females, but not shown here.) Although we cannot simultaneously adjust for all these factors from the data at hand, some indication of the effect of the employed-unemployed dimension on reports of diseases and disabilities may be inferred from Table 4. The effect of differences in age distributions by employment status or directness of interview on number of reported diseases may well mask a much more profound effect due to smoking or, quite to the contrary, cause such an effect to appear when none actually exists. Considering the profound differences in age distribution existing between employed and unemployed members of the sample or between direct and proxy respondents, it is difficult to judge what indirect age adjustment actually accomplished. It would have been more appropriate under the circumstances to use a direct age adjustment method or compare age-specific disability rates. (All other reports on the same data published by NCHS do report more detailed age-specific rates or use a direct method of age adjustment that reflects age-specific rates more directly than the indirect method of age adjustment used only in this report and no other. This report does present age-specific data, but for large age ranges as 17 to 44, 45 to 64, and over 65 years, which is really not of much help.) Detailed age-specific rates then should have been shown and adjusted for influences on responses due to employment and proxy status at the very least.

AGE DISTRIBUTION OF MALES—BY EMPLOYMENT STATUS AND BY DIRECTNESS OF INTERVIEW[a]



[a] From data supplied by the National Center for Health Statistics.

3.3 How Many Smokers Are There?

The prevalence of smoking in the NHS sample is of prime importance since, after all, smoking is the independent variable in the comparison. Yet, nowhere do we find an attempt to assess the accuracy with which numbers of smokers or non-smokers were obtained. There are two well-known studies available that make comparable observations of the distribution of smoking in the U. S. population. It is interesting that both differ quite emphatically from the age distribution of smokers and non-smokers obtained from the household interview [5, 7]. These differences are summarized in Table 5. Again, the difference is much larger and much more pronounced among males than females, most likely because there were many more proxies among the former.

These data need not indicate that the NCHS survey was plagued by exceptionally large errors in counting smokers and non-smokers. After all, the error may have been in Hammond's or Hearzel's studies. However, it is

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Table 4. PERCENT OF SAMPLE POPULATION EXPERIENCING DISABILITIES, BY EMPLOYED AND UNEMPLOYED[a]

Employment status	Bed confinement last two weeks	Bed confinement last year	Restricted activity last two weeks	Short Hospital stay last year	One or more chronic conditions	Three or more chronic conditions
			Males			
Employed	3.8	11.0	7.7	7.7	54.2	11.5
Unemployed	7.9	19.5	30.3	12.8	69.9	30.6
			Females			
Employed	5.7	13.9	10.0	11.3	55.8	14.9
Unemployed	8.1	18.0	15.4	18.6	66.0	25.5

[a] From data supplied by the National Center for Health Statistics.

clear that even for such a simple question as whether an individual has ever smoked, large errors appear if a data gathering procedure relies heavily on proxies. Again, it would have been important for the credibility of the study if more attention had been given to the accuracy of smoking histories and discrepancies between the survey's results and that of other studies examined.

4. CONCLUSIONS

Surely it is important to know to what extent smoking harms the population of this country. It may be even that given existing budget limitations, better methods of inquiry than a household sampling survey may not be available. Yet, it hardly helps to clarify this problem if data resulting from methods that are known to produce

Table 5. COMPARISON OF NON-SMOKERS' AGE DISTRIBUTION[a]

Sex and age group	Number of non-smokers from NHS [a]	Number of non-smokers expected according to Heanszel, et al. [b]	Percent difference between observed and expected for Heanszel, et al.	Number of non-smokers expected according to Hammond [c]	Percent difference between observed and expected for Hammond
Males					
18-24	4,396	3,721	15%	--[d]	--[d]
25-44	4,926	4,734	4	--[d]	--[d]
45-64	4,406	5,274	20	5,483	24%
65+	3,299	4,376	33	3,913	18
Females					
18-24	6,765	6,691	1	--[d]	--[d]
25-44	11,019	12,740	16	--[d]	--[d]
45-64	11,723	14,490	23	13,259	12
65+	8,250	8,756	6	8,666	5

[a] As obtained from household interviews with the expected number of non-smokers based on two studies of tobacco smoking patterns of the U.S. population.
[a] *Source:* [10, Table 1, pp. 23–4].
[b] *Source:* [7].
[c] *Source:* [5].
[d] Not given.

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large errors and are possible sources of bias are subjected to inadequate and perhaps inappropriate analyses and not enough attention is paid to the potential influences of various aspects of the survey methods on these findings. Perhaps if any lesson is to be learned from this issue, it is not that smoking causes untold diseases and disabilities and loss from work, but that claims about such controversial topics need to be carefully and intelligently reviewed, even if they are made by public agencies or by other generally reliable sources.

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A prospective study of 973 men born in 1913 in Göteborg, Sweden, was undertaken in 1963 (*51, 52*). The proportion of myocardial infarctions among cigarette smokers was significantly greater than among nonsmokers ($P < .05$), and the incidence of myocardial infarction rose with increasing cigarette consumption (table 1). Of the 35 individuals who experienced a myocardial infarction between 1963 and 1970, only two had been nonsmokers; in the whole population of men born in 1913, 56 percent were smokers.

Although angina pectoris was more common in smokers than nonsmokers, the difference was smaller than for myocardial infarction and was not statistically significant (*52*).

Paffenbarger, et al. (*42*) reported on the health experience of 3,263 longshoremen studied over the past 18 years. During this interval 1,698 were known to have died, 350 dying from CHD. Longshoremen who smoked more than 20 cigarettes a day faced a risk of coronary death which was more than twice as great as that of the group made up of both nonsmokers and smokers of less than 20 cigarettes a day ($P < .01$).

Keys, et al. (*30*) analyzed the 20-year CHD incidence among 279 Minnesota men aged 47 through 57 years who were CHD free at entry into the study. The relationship of cigarette smoking habits at the start of the study to the subsequent incidence of CHD was examined. The originally published table of results was incorrect and the authors have supplied a corrected table which appeared in a later issue of the same journal (table 2). The morbidity ratio for "hard CHD" (CHD deaths plus myocardial infarctions not resulting in death) among those smoking more than 10 cigarettes a day is similar to that reported from the large prospective studies. However, with the small number of cases in each smoking category, there are no statistically significant differences in the incidence of CHD between the categories, either singly or combined.

Retrospective studies of CHD have recently been reported from Czechoslovakia, Sweden, Norway, and India which corroborate earlier studies linking cigarette smoking with excess CHD morbidity and mortality.

TABLE 1.—*Incidence (1963–1970) of heart infarct in relation to tobacco consumption in "The Men Born in 1913," Göteborg, Sweden.*

n = 855

Smoking classification	Heart infarct Number	Heart infarct Percent
Never smoked n = 207	(2)	1.0
Stopped smoking n = 168	(2)	1.0
Cigarette smokers	(13)	6.0
1–14 cig/day n = 234		
15–24 cig/day n = 138	(9)	7.0
≧25 cig/day n = 33	(4)	12.0
Pipe/cigar n = 75	(5)	7.0

SOURCE: Tibblin, G., Wilhelmsen, L. (51).

TABLE 2.—*Cigarette smoking at entry and subsequent 20-year CHD incidence among Minnesota men.*[1]

Age	Number of men	Item	Never	Smoking habit (cigarettes/day) Stopped	<10	10–19	>20
47,48	53	% with habit	23	19	9	19	30
49,50	51	% with habit	33	20	14	10	23
51,52	69	% with habit	33	26	14	14	13
53,54	53	% with habit	36	30	8	13	13
55–57	51	% with habit	24	33	8	18	17
47–57	277	Number of men	83	71	30	41	52
47–57	277	Hard CHD rate (%)	12.0	15.5	10.0	17.1	21.2
47–57	277	Hard CHD rate (SE)	± 3.6	± 4.3	± 5.5	± 5.9	± 5.7
47–57	277	Hard CHD Morbidity Ratio	1.00	1.29	.83	1.43	1.77
47–57	277	All CHD rate (%)	±21.7	±21.1	±16.7	±19.5	±26.9
47–57	277	All CHD rate (SE)	± 4.5	± 4.8	± 6.8	± 6.2	± 6.1
47–57	277	All CHD Morbidity Ratio	1.00	.97	.77	.90	1.24

[1]Cigarette smoking habits, by age at start of the 20-year follow-up, 20-year incidence rates (per 100 men), and standard errors (SE) of the rates. "Hard CHD"—CHD death and myocardial infarct. "All"—angina pectoris and other CHD diagnoses. "Deaths"—from all causes except violence.

SOURCE: Modified from Keys, A., et al. (30).

(51) Tibblin, G., Wilhelmsen, L. Rökningen som riskfaktor. (Smoking as a risk factor.) Lakartidningen 68(7): 637–639, February 10, 1971.

(52) Tibblin, G., Wilhelmsen, L. Rökning och koronarsjukdom (5): 1913 års män. (Smoking and coronary disease (5): Men born in 1913.) Läkartidningen 67(2): 151–155, January 7, 1970.

(42) Paffenbarger, R. S., Jr., Gima, A. S., Laughlin, M. E., Black, R. A. Characteristics of longshoremen related to fatal coronary heart disease and stroke. American Journal of Public Health and the Nation's Health 61(7): 1362–1370, July 1971.

(30) Keys, A., Taylor, H. L., Blackburn, H., Brozek, J., Anderson, J. T., Simonson, E. Mortality and coronary heart disease among men studied for 23 years. Archives of Internal Medicine 128(2): 201–214, August 1971. (Table 2 modified by personal communication October 1971.)

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The Prague study (19) included 443 men between the ages of 60 and 64 years. Significantly more ($P < .05$) individuals with a "probable" myocardial infarction were found among cigarette smokers than among nonsmokers or pipe and cigar smokers.

The smoking habits of 120 patients with myocardial infarction who were hospitalized in Göteborg were compared with those of the entire "men born in 1913" population sample (17, 62). A significantly ($P < .01$) greater number of smokers and heavy smokers (more than 15 cigarettes a day) were found in the myocardial infarction group than in the population sample.

The Bergen, Norway, cross sectional study of 2,117 women and 2,472 men documented a relationship between smoking and CHD in men, which was most marked in the 50 to 59 year old age group (16). No effect of smoking on the prevalence of CHD in women was demonstrable in this study, and the effect in men did not appear to be related to the daily number of cigarettes smoked.

In New Delhi, 100 "well documented" cases of ischemic heart disease were compared with an equal number of control cases (8). In this study, significantly more ($P < .01$) of the case group smoked cigarettes regularly than the control group (Morbidity Ratio = 2.1).

Mulcahy, et al. (40) recently found a positive association between coronary heart disease mortality rate and calculated per capita cigarette consumption in 21 countries. He interpreted the results as being consistent with the hypothesis that cigarette smoking is a significant risk factor in CHD mortality.

Stamler, et al. (50) found that for both men and women the 1964 CHD mortality rates in 17 developed countries were related to average annual per capita cigarette consumption.

(19) Fodor, J. Rökning och koronarsjukdom (4): Pragstudien. (Smoking and coronary disease (4): The Prague Study.) Läkartidningen 67(2): 150–152, January 7, 1970.

(17) Elmfeldt, D. Rökning och koronarsjukdom (8). Rökvanor hos patienter med hjärtinfarkt. (Smoking and coronary disease (8): Smoking habits of patients with heart infarctions.) Läkartidningen 67(2): 168–169, January 7, 1970.

(62) Wilhelmsen, L. The myocardial infarction clinic in Göteborg—organization and preliminary results. Pehr Dubb Journalen 3: 43–51, 1969.

(16) Eilertsen, E., Sulheim, O. Rökning och koronarsjukdom (3): Bergenstudien. (Smoking and coronary disease (3): The Bergen Study.) Läkartidningen 67(2): 145–149, January 7, 1970.

(8) Bansal, R. D., Chablani, T. D., Gulati, P. V. An epidemiological study of ischaemic heart disease in patients attending the cardiology clinic at the AIIMS, New Delhi. Indian Medical Journal 64(4): 81–92, April 1970.

(40) Mulcahy, R., McGilvray, J. W., Hickey, N. Cigarette smoking related to geographic variations in coronary heart disease mortality and to expectation of life in the two sexes. American Journal of Public Health and the Nation's Health 60(8): 1515–1521, August 1970.

(50) Stamler, J., Stamler, R., Shekelle, R. B. Regional differences in prevalence, incidence and mortality from atherosclerotic coronary heart disease. IN: deHaas, J. H., Hemker, H. C., Snellen, H. A. (Editors). Ischaemic Heart Disease. Leiden, The Netherlands, Leiden University Press, 1970. pp. 84–127.

INTERACTION OF SMOKING AND OTHER RISK FACTORS

The Report of the Inter-Society Commission for Heart Disease Resources summarized the evidence indicating that three risk factors (hypercholesterolemia, hypertension, and cigarette smoking) are properly designated major risk factors for premature CHD (28). Other possible risk factors including obesity, physical inactivity, diabetes mellitus, elevated resting heart rate, electrocardiographic abnormalities, a positive family history of premature CHD, and psychologic and social factors have also been described (54, 55, 56).

In the study of 973 men born in 1913 in Göteborg, Sweden, several coronary risk factors including elevated serum cholesterol, elevated serum triglyceride, low physical activity at work, and smoking were found to be related to an increased risk for the development of coronary heart disease during the subsequent years of the study. Failure to find a relationship between hypertension and an increased risk of CHD may have been due to the fact that all patients with hypertension in 1963 have been under treatment since that time.

Tibblin and Wilhelmsen (52) found that as a patient accumulated more risk factors his chance of developing CHD became substantially greater. Werkö (61) reported from the same Göteborg study that patients who were smokers, had sedentary jobs, and had both elevated cholesterol and triglycerides experienced a 4-year incidence of new coronary events of about 20 percent; the 4-year incidence among those who exhibited only one or two risk factors was much lower, ranging from 0 to 3 percent. ECG changes and anginal pain were included in the definition of new coronary events.

Paffenbarger, et al. (42) evaluated coronary risk factors in the study of 3,263 longshoremen. They found that, with the exception of diagnosed heart disease, smoking was the most important factor predictive of high risk for coronary mortality.

Keys, et al. (30) in the study of 270 Minnesota men, concluded that a positive cold pressor test, elevated serum cholesterol, and elevated systolic blood pressure had major predictive power for CHD death or infarction; in their analysis smoking seemed less important.

(28) Inter-Society Commission for Heart Disease Resources. Atherosclerosis Study Group. Epidemiology Study Group. Primary prevention of the atherosclerotic diseases. Circulation 42(6): A55–A95, December 1970.

(55) U.S. Public Health Service. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. Washington, U.S. Department of Health, Education, and Welfare, Public Health Service Publication No. 1696, 1968. 117 pp.

(61) Werkö, L. Can we prevent heart disease? Annals of Internal Medicine 74(2): 278–288, February 1971.

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Epidemiologic Studies. The study of (42) Paffenbarger et al. show more than what is stated in pages 462 and 463. The smoking data refers only to the less active shoremen. Furthermore, the group was artificially divided into high-and-low-risk groups and the mortality rate was greater for individuals who were less active than for cargo handlers. Portions of the Results and the entire Summary are as follows:

- As already shown, less active longshoremen sustained a death rate 27 per cent higher than cargo handlers. Smoking one or more packs of cigarettes per day doubled the risk of coronary death over that for smoking less or not at all. Risk among men with systolic blood pressure above mean levels exceeded that among those with lower levels by 84 per cent. An excess death rate of 23 per cent accompanied longshoremen with body weight above mean levels as compared with the rate for those less hefty. Men with diagnosed heart disease sustained a coronary death rate 168 per cent higher than that for peers without such diagnosis. (Although not shown in the figure, the corresponding excess for men with diagnosed coronary heart disease was 267 per cent.) And last, although not statistically significant, an excess death rate of 44 per cent attended men with abnormal glucose metabolism over that for those with normal glucose metabolism.

- These first-order relationships between six characteristics of high risk and coronary mortality suggest a rank order by declining strength of: diagnosed heart disease, cigarette smoking, higher blood-pressure level, less strenuous work activity, heavier weight-for-height, and abnormal glucose metabolism. Although a history of heart disease carries a higher risk-ratio for coronary death, it has less public health significance than either cigarette habit or higher blood-pressure level because of its lower prevalence.

Summary

We identified 350 decedents from coronary heart disease and 93 from stroke among 3,263 longshoremen in an 18-year follow-up after multiphasic screening examinations. Men with physically less active jobs, who expended 925 fewer calories per work day, sustained coronary death rates one-quarter higher than cargo handlers. Differences in coronary mortality were largest at younger ages and decreased steadily to disappearance at older ages.

Splitting the population into presumed high- and low-risk groups sorted out four other characteristics associated with coronary mortality: pre-existing heart disease, systolic blood pressure above mean levels, cigarette smoking of one or more packs per day, and weight-for-height above mean levels. The risk of coronary mortality accompanying each of these characteristics was greater for individuals who were less active than for cargo handlers.

Longshoremen with more sedentary jobs sustained stroke death rates similar to those of cargo handlers in the 18-year follow-up. Three other characteristics, however, identified groups at high-risk of stroke mortality: pre-existing heart disease, systolic blood pressure above mean levels, and abnormal glucose metabolism.

The association between work activity and coronary mortality, when considered with the lack of such association with stroke mortality, suggests that physical activity influences the myocardium or its function more than the atherosclerotic process.

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Cholesterol Levels. The importance of cholesterol levels in the blood mentioned in this page and in the next three pages has recently been questioned by Oster (Med Counterpoint 4: 13-27, 1972). The questions raised by the author relate to the value of epidemiologic studies in general. The article is reporduced in its entirety.

Oster K A: Prevention of atherosclerosis.

EDITOR'S NOTE: *Dr. Oster's paper takes issue with certain conclusions of the Inter-Society Commission Report that have been drawn from the Framingham Study concerning the risk of coronary heart disease. It particularly challenges the stated relative effect on risk of CHD at different levels of serum cholesterol. Some of the questioning is based on clinical experience confirmed by others (e.g., the unimportant effect on serum cholesterol levels of significant reductions in dietary cholesterol).*

Moreover, Dr. Oster casts doubt on the value of epidemiologic studies of this type and questions the mathematical underpinnings of the statistical methods employed in this case. To review such matters we have called upon a consulting mathematician to offer a critique of Dr. Oster's remarks as well as the methodology of the Framingham Study. His comments immediately follow Dr. Oster's paper.

In December 1970, The Inter-Society Commission for Heart Disease Resources, "comprised of outstanding leaders in the field of cardiovascular diseases and representatives of national professional organizations capable of making significant contributions," reported its suggestions for the prevention of atherosclerotic diseases.

Dr. Oster is Chief of Cardiology, Park City Hospital, Bridgeport, Conn. The author gratefully acknowledges the assistance of Michael A. Berger in the mathematical analysis of the statistical data in the Report. Mr. Berger, a student at the University of Bridgeport, was supported in this work by a research grant from the Greater Bridgeport Heart Association.

*"Primary Prevention of the Atherosclerotic Diseases": Report of the Inter Society Commission for Heart Disease Resources, Circulation 42 A:55, 1970

The Commission was created through a contract with Regional Medical Programs Service to help fulfill the requirements of Section 907 of Public Law 89-239, which established the Regional Medical Programs in 1965. The Commission worked under contract No. NH 69-29 with the Health, Science, and Mental Health Administration Department of the Department of Health, Education and Welfare. The funds came out of taxpayers' money.

In its introductory note to the reader, the Commission invites constructive criticism of the work of its study groups, particularly those who attempt to apply these guidelines. In the following paper such constructive criticism will be given and it will be shown that the Report of the Commission is prejudicial, based on dubious data and therefore probably deceptive. Furthermore, by thus wasting the taxpayers' money, the Report of the Commission, instead of advancing the cause of coronary heart disease prevention, channels the research funds overwhelmingly into narrow, preconceived, subjective, discredited areas of research. It thereby hinders, if it does not preclude, the development of other approaches which may provide more effective solutions of this problem, so vital to the health of the American people.

To the tune of scheduled press conferences and through recourse to the various media, the American people were advised to change their diets drastically and especially curtail the consumption of cholesterol to 300 mgs. daily from the usual 600 mgs. and reduce the intake of saturated fats to 35% from 40%. Admittingly having no proof on which to base these revolutionary recommendations that

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TABLE I

ESTIMATED RELATIVE REDUCTION IN CORONARY HEART DISEASE INCIDENCE (v) ASSOCIATED WITH RELATIVE REDUCTION IN SERUM CHOLESTEROL (u)

Relative decrease in serum cholesterol (u)	Relative decrease in coronary heart disease incidence (v)	Relative decrease in serum cholesterol (u)	Relative decrease in coronary heart disease incidence (v)
[illegible]	.026	.26	[illegible]
[illegible]	[illegible]	[illegible]	.567
.03	.075	.28	.583
.04	.103	.29	.598
.05	.128	.30	.613
.06	.152	.31	.627
[illegible]	.176	.32	.642
[illegible]	.199	.33	.655
[illegible]	[illegible]	.34	.669
[illegible]	.244	.35	.682
[illegible]	.267	.36	.695
[illegible]	.288	.37	.707
.13	.310	.38	.720
[illegible]	.330	.39	.731
.15	.351	.40	.743
.16	.371	.41	.754
[illegible]	.391	.42	.765
[illegible]	.410	.43	.776
[illegible]	.429	.44	.786
[illegible]	.448	.45	.796
.21	.466	.46	.806
[illegible]	.484	.47	.815
.23	.501	.48	.824
.24	.518	.49	.833
.25	.535	.50	.842

Note: Values of v were obtained from relationship, v = 1 − (1 − u)[illegible] [illegible] in Fed. Proc. 21 (Suppl. No. 4) [illegible] July–August, 1962.

[illegible] data illustrate the potential for prevention and the possibility of [illegible] declines in CHD morbidity [illegible]. For example, a ten percent reduction in serum cholesterol level of the U.S. population (u = .10) is estimated to yield a 24.4 percent decrease in CHD incidence (v = .244).

[illegible] affect the life habits of the American people [illegible] alter the normal [illegible] of [illegible] foods and the [illegible] of livestock, the Commission presents some [illegible] facts, studies, and tables to support their [illegible] theories.

On page A-8 of the Commission's Report[1] we [illegible] Table 16: "The Estimated Relative Reduction [in] Coronary Heart Disease Incidence Associated [with] Relative Reduction in Serum Cholesterol" [re]numbered as Table I of this article above. The [values] of v were obtained from the relationship [illegible] [illegible] described in a study of Corn[field] where v is the relative incidence of CHD and u is the relative serum cholesterol level. An example is given that a 10% reduction in the serum [cholesterol] level in the United States population [(u =] .10) is estimated to yield a 24.4% decrease in [coronary] heart disease incidence (v = .244).

Since such pivotal importance is ascribed to this table and since it is utilized in two prior studies [illegible] we deemed it worthwhile to re-read Cornfield's original work and find out if the statements contained therein correspond with the table published by the Inter-Society Commission. In the entire study of Cornfield, we were unable to find the equation v = 1 − (1 − u)[illegible] but we do find equation (7): P = .0094$\left(\frac{Y_1}{100}\right)^{[illegible]}\left(\frac{Y_2 - 75}{100}\right)^{[illegible]}$ where Y_1 and Y_2 are serum cholesterol and systolic blood pressure respectively.

Cornfield states, "A 1% decrease in cholesterol would be associated with a 2.60% decrease in risk of coronary heart disease throughout the range of cholesterol values." In other words, it is not just limited to the levels of frank hypercholesterolemia, but also applicable to the lower values of cholesterol in the serum without exception. So, if to drive this point home by *reductio ad absurdum*, a lowering of cholesterol level from a normal of 220 mgs to 110 mgs percent would put a theoretical person at an 81% less risk of coronary heart disease: the same as if lowering the cholesterol from 480 mgs. to 240 mgs per cent, providing that the experimental reduction of cholesterol is of the same risk, a condition that the Commission fails to mention.

Cornfield states in a personal letter: "My paper, 'Joint Dependence of Risks of Coronary Heart Disease on Serum Cholesterol and Systolic Blood Pressure: a Discriminant Function Analysis' (Fed. Proc. 21, Suppl. No. 4, pp 58-61, July–August, 1962) states, 'If one could lower cholesterol levels by a given amount, say 15%, and if equation (7) describes not only the association between risk and cholesterol level in Framingham, but also the change in risk that would accompany an experimental alteration in serum cholesterol, then the relative risk would be [illegible], or a reduction of about 35%.'" Mathematical analysis reveals Cornfield's formula correct insofar as statistical significance is concerned.

Having shown the biological impracticability of the Report's Table 16, we turn to the collection of data for Cornfield's equation. We question this data which was given to him by the Framingham Study and the paucity of numbers from which

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TABLE II[3]

NEW CHD IN 6 YEARS FOLLOW-UP: ACTUAL AND EXPECTED NUMBER OF CASES AMONG MEN 40-59

Serum Cholesterol mg/100 cc.	Systolic B.P. mm Hg.	NEW CHD		Population at Risk
		Expected*	Actual	
200	Total	10.5	12	319
	<117	0.8	2	53
	117-126	1.4		66
	127-136	1.8	2	59
	137-146	2.3	1	65
	147-156	1.6	2	37
	157-166	0.7	1	13
	167-186	1.4	3	21
	187+ over	0.5	1	5
200-209	Total	5.9	2	133
	<117	0.5		21
	117-126	0.8	2	27
	127-136	1.4		34
	137-146	1.0		19
	147-156	1.9		16
	157-166	0.7		10
	167-186	0.4		5
	187+ over	0.1		1
210-219	Total	6.9	6	121
	<117	0.4		15
	117-126	0.9	1	25
	127-136	1.0	2	21
	137-146	1.5		26
	147-156	0.4		6
	157-166	0.9		11
	167-186	1.1		11
	187+ over	0.8	3	6
220-244	Total	22.3	23	334
	<117	0.6		20
	117-126	2.9	8	69
	127-136	4.7	2	83
	137-146	5.5	6	81
	147-156	2.4	3	29
	157-166	1.5	1	15
	167-186	3.1	2	27
	187+ over	1.6	1	10
245-259	Total	11.6	8	136
	<117	0.5		14
	117-126	1.3		24
	127-136	2.3		33
	137-146	2.0	3	23
	147-156	1.9	2	19
	157-166	1.3		11
	167-186	0.7	2	5
	187+ over	1.5	1	7
260-284	Total	16.0	23	156
	<117	1.0	1	22
	117-126	1.4	5	22
	127-136	2.1	2	26
	137-146	3.5	2	34
	147-156	1.9	4	16
	157-166	1.7	2	13
	167-186	2.7	6	15
	187+ over	1.5	1	7
285+ over	Total	18.9	18	130
	<117	0.7		11
	117-126	1.7	1	19
	127-136	3.1	4	28
	137-146	3.1	4	23
	147-156	2.8	1	16
	157-166	2.5	4	12
	167-186	3.2	3	14
	187+ over	1.9	1	7

*Expected number of cases = $\frac{\text{(population at risk)}}{(1 + e^{[\text{constant} + \text{coefficient} \times \text{cholesterol} + \text{coefficient} \times \text{systolic B.P.}]})}$

Note: Cholesterol determinations were done by the Kendall-Abel method at Framingham, Massachusetts

he derived his equation. We doubt the validity of the application of Cornfield's equation to Table 16 in the Inter-Society Report in view of the latter's simplifications and the omission of the risk of experimental alteration in serum cholesterol levels which Cornfield mentions. According to the Commission's attitude, this risk would be zero. The Commission implies that the reduction mentioned in the footnote to Table 16 would only be valid for the very high levels of serum cholesterol found in hypercholesterolemia, but Cornfield claims his formula is valid for the whole range of cholesterol levels.

A total of 1329 male persons between the ages of 40 to 59 were examined for freedom of coronary heart disease in the Framginham Study. Neither then (1962) nor at the present time can even the most astute diagnostician say with certainty that an individual is free of coronary heart disease. So one of the basic assumptions of the Framingham Study is open to serious doubt.

Of the 1329 allegedly coronary heart disease-free persons only 92 developed various incidents of coronary heart disease, which must have included angina pectoris. Seventy-four were distributed over a range of cholesterol from 200 to 284 mgs per cent, with groupings as high as 23 to a low of 2 persons. The groupings were arbitrarily chosen as shown in Table II reprinted from Cornfield's paper (see at left). A questionable transformation takes place by semantic legerdemain on the part of the Commission. The *risk* of coronary heart disease in 92 persons out of a group of 1329 reported by Cornfield is equated by the Commission to the *incidence* of coronary heart disease in many millions of the U.S., if not the world's, population — a substitution which is unacceptable. Again, we doubt the accuracy of the data presented to the computer.

It is a known fact that cholesterol in the non-fasting individual, as tested in Framingham, is not greatly affected by dietary intake of fats and cholesterol in the short run. From values of our own study, described below, as well as from the world literature we learn that the same individual has variable values of serum cholesterol on different days, different seasons and other circumstances.[3]

Cholesterol was determined in five males and five females of an age group from 18 to 30 on two different occasions. On one occasion a low caloric breakfast was served consisting of two ounces of Ovaltine** dissolved in twelve ounces of milk.

**Ovaltine contains protein (10%), easily emulsified fat (1%) and carbohydrates (75%). Each teaspoonful contains 22 calories.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

TABLE III

SCATTERED VALUES OF SERUM CHOLESTEROL IN A GROUP OF INDIVIDUALS AT VARIOUS TIMES

Key:

○ = Low caloric diet, fasting
□ = High caloric diet, fasting
◉ = Low caloric diet, post-prandial
◘ = High caloric diet, post-prandial

Group A–G is male **Group H–N is female**

Patient→ Serum Level ↓	A	B	C	D	E	F	G	H	I	J	K	L	M	N
150–159										◘				
160–169		◘												
170–179				◉	□					□	□◘			
180–189			□		○□◉	□				◉				□
190–199		○◉	◘	○				□◘		○	○			◘
200–209			◉	◘		◘					◉		□◘	
210–219		□	○	□			◘	○◉						
220–244	◘						□		C□◉			○□◘		
245–259	◉								□			◉		
260–284	○□													

Note: Accuracy of determinations, by the Libermann-Burchardt method, was ±3.5%.

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Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

On a subsequent day a high caloric breakfast consisting of bacon, eggs, sausages, bread, butter, and orange juice was consumed. Post-prandial blood specimens were examined 15 minutes after the individual finished eating the low caloric meal. Ninety minutes after the high caloric meal post-prandial blood specimens were examined. Four individuals (2 males and 2 females) aged between 30 and 62 consumed the high caloric meal with an addition of 2 ounces of Ovaltine® in 12 ounces of milk. Fasting and 90 minutes post prandial specimens were examined. There was a total of 48 different cholesterol determinations.

It was found that only eight times did the fasting and post prandial specimens pair (see Table III, page 00). The other pairs of fasting and post-prandial values varied significantly in the same individual and projecting this finding to the Framingham Study, 66% of the post-prandial values used in this population group might be subject to grouping changes—a factor that would throw the application of Cornfield's equation to the Framingham Study into serious doubt.

The Framingham blood specimens were taken when convenient to the volunteers regardless of diet, time of the day, or other anamnestic influences. The accuracy of our determinations was ±3.5% as determined by duplicates. If hypercholesterolemia is defined as serum values over 260 mgs per cent, only one individual had such a fasting serum value, and that went down 20-40 mgs per cent post-prandially, jumping two of Cornfield's sample groups. It is also quite presumptuous to project or generalize findings found in a homogeneous northeastern community whose racial and ethnic background is not given and which could have completely different eating habits to embrace the considerable diversity of the United States population. It has been reported by others in epidemiological studies that the death rate from coronary heart disease is different in various states of the Union.[4]

Due to the narrow range chosen by Cornfield in his groupings, an individual's cholesterol level could shift from one of Cornfield's cholesterol groups into another, from day to day, and week to week. This would also apply to blood pressure measurements. These shifts would then raise havoc with Cornfield's formula. Again we find Cornfield's formula palpably wanting biologically though statistically valid, assuming the constancy of starting values.

Cornfield also stresses the fact that the percentage reduction of cholesterol pertains to risk of coronary heart disease in all values of the table high or low. But it is different if one considers the presentation of risk in actual milligram per cent reduction. There we have a large absolute difference in risk when added to a large, rather than to a small, initial level of serum cholesterol.

With complete disregard of the above considerations, the Commission devised its own interpretation of Cornfield's data. Instead of *risk*, we are now told that the coronary heart disease *incidence* is reduced with a relative reduction in serum cholesterol. According to Webster's Dictionary, 2nd edition, risk and incidence have two completely unrelated meanings—

Incidence: act, fact, manner of falling upon or affecting, range of occurrence or influence
Risk: degree of probability of loss or chance of loss

We are now told that a 10% reduction of cholesterol in the population of the United States will yield a decrease of 24.4% in the *incidence* of coronary heart disease. From Table 16 in the Commission's report we can learn that a 50% decrease in serum cholesterol will yield a decrease of 84.2% of the *incidence* of coronary heart disease. Any biologically oriented researcher knows that this is a physiologic impossibility and is absurd in its implication because a 50% reduction of serum cholesterol levels may entail untold dangers.

Cornfield must have sensed these shortcomings because in a later (1969) publication[5] he stated, "We must admit at the outset that we have no secure basis for estimating the reduction in incidence of or mortality from coronary heart disease that could be achieved by application of current knowledge." He also states in the same article, "It seems clear that despite a very considerable scientific effort and some tantalizingly suggestive results, we have no clear-cut generally accepted answer to the question whether cholesterol lowering measures can affect coronary heart disease." We concur in Cornfield's doubts. We feel that his equation is not valid biologically and should not be used to substantiate the implied effect of proposed dietary changes suggested by the Commission.

Obsessed with the idea of correlating values from blood chemistry with actual disease, the Commission was undisturbed by reality and objectivity. Since the Commission's mind was made up in advance, the membership of the Commission did not want to be bothered with the confusing facts. For example, in a study of cigarette smoking, the find-

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ings of Keys and others[2] that there was no connection between cigarette smoking and coronary heart disease in certain European countries was not mentioned, whereas the findings concerning the relationship between cholesterol levels and coronary heart disease in the same study are given prominence. Keys also states in the same study, again not mentioned in the Commission's Report, that the incidence of coronary heart disease is lower among individuals who smoke less than 20 cigarettes per day than among *nonsmokers* or heavy smokers. An unbiased report would not have selected from such omissions.

In a very recent study by Keys[3] we find that in contrast to a value of 2.66 found in the Framingham Study as the exponent for coronary heart disease incidence, a value of 2.21 has now been established. There is also a presentation that angina pectoris was less closely related to serum cholesterol level than it was to myocardial infarction. This result is also duplicated by a study of Western Electric Co employees and Los Angeles civil servants.[4] However, as mentioned before by Gofman in his paper,[5] all phases of coronary heart disease are included in the Framingham Study. This again shows the unreliability of his original data.

Furthermore, the statements of Pearce and Dayton,[6] who warn that their findings are not to be construed as recommending reductions in the American diet, are alarmingly absent in the Commission's Report. Due to their caveats a potential danger from unregulated fats in the commercial market is underplayed. The American people are led to believe that unsaturated fatty acids do not undergo chemical changes such as hydrogenation during cooking—the truth of such claims is not even known in the Inter-Society Commission Report.

If publications of the individual members concerning the Commission are examined, one finds that in July 1970 J. J. Dixon wrote an editorial "in the Annals of Internal Medicine" about the prevention of coronary heart disease.[7] The conservative physician must agree that although the data is suspect, the conservative and the fundamental principle that he should do no harm. In December of the same year one finds Dixon a member of the Commission giving his opinion to newspaper reporters on modifications of dietary changes.

A more cautious view of such dietary changes is reflected in the remarks of Dr. Donald S. Fredrickson, who chaired the Inter-Society Commission Report in his St. Cross Lecture[8] at the National Heart Hospital at the Royal College of Physicians of London, published in the British Medical Journal:[9]

> "Here are some things about the report to be pondered in the light of what is actually known. The unproven comparison of cholesterol and fats versus heart disease stands. What evidence do we have that an egg a day spells peanuts for all Americans? . . .
>
> ". . . One looks vainly in the Commission Report for a thing new and strong enough to change the present governmental position concerning dietary fat modification. . . ."

The Commission disregards the potential economic dislocations which would result from their recommendations, should they become realized. It also completely disregards the warnings and excellent deliberations in the Report of the Ad Hoc Heart Review Panel of the National Heart Institute dated June 1960 and published as American Heart Association Monograph No. 28, 1969, which antedates the Inter-Society Commission Report. The members of that panel have at least the same scientific standing and authority, but act more responsibly than the members of the Inter-Society Commission.

By critical analysis of the Report of the Inter-Society Commission for Heart Disease Resources concerning the prevention of atherosclerosis we are led to endorse the opinions of Ludwig and Co-Workers[10] "Errors of presentation include inappropriate generalizations and the incautious use of unevaluated data." We feel that the Commission presented its findings in a misleading manner.

We quote again from Ludwig and Co-Workers[10] "More serious consequences follow when erroneous conclusions are drawn from invalid data or from faulty or incomplete analyses. Health programs may be augmented or discontinued, beneficial practices modified, and worthless solutions to problems advanced, all on the basis of misinformation."

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15. Ludwig, J., and Colbert, J.: "Some Miseries of Health Statistics," *JAMA* 216: 481, 1971.

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Stamler (*49*) has analyzed the data on 13 deaths occurring during the first years of the Chicago Coronary Prevention Evaluation Program, which originally consisted of 519 coronary-prone male volunteers aged 40 to 59 who were free from clinical CHD. Eleven of the 13 decedents had three or more coronary risk factors at entry into the program, and at least 8 were cigarette smokers at the time of death. Forty-three men, who were cigarette smokers at entry into the Coronary Prevention Evaluation Program, gave up smoking and have remained active in the program. There have been no deaths from cardiovascular causes in this group. Stamler (*49*) commented: "Even though the number of decedents was small, these data strongly suggest that continued cigarette smoking is associated with very high risk of premature death for very coronary-prone men, and that other preventive measures are by themselves of limited value for them as long as they fail to give up cigarette smoking."

As described in the 1971 report, "The Health Consequences of Smoking" (*56*), some studies have indicated that smokers show increased levels of serum lipids while others have not. Such contradictory results are also present in recent studies from Germany, Poland, and Sweden (*21, 39, 53*).

After a patient suffers a myocardial infarction, he frequently gives up smoking (*17, 26*). Only fragmentary data are available on what effect the cessation of cigarette smoking might have on the likelihood of a recurrent myocardial infarction (*9, 34, 43*). Ninety-two survivors of a first myocardial infarction were studied over a 3-year period by Parás Chavero, et al. (*43*). During this time, 37 patients continued smoking, and 12 of them (32 percent) experienced a second myocardial infarction. The 51 patients who did not smoke during this 3-year period included 39 ex-smokers and 12 patients who had never smoked. Eight of the nonsmokers (16 percent) experienced a second myocardial infarction. The smoking habits of four of the patients were not known. Although the continuing smokers experienced a greater rate of recurrent myocardial infarction than the nonsmokers, the difference was not statistically significant ($P = .07$).

The role of genetic factors in the development of CHD and the difficulties associated with the use of twin studies were discussed in the 1971 report, "The Health Consequences of Smoking" (*56*). Mailed questionnaires were used to establish the diagnosis of angina pectoris in a study by Lundman, et al. of twin pairs discordant with respect to smoking habits and in a study by Liljefors of twins with CHD. Lundman, et al. (*36*) recently investigated 69 male twins with the diagnosis of angina pectoris established by questionnaire. Only 22 percent of these diagnoses could be verified by clinical examination.

In a study of CHD, Liljefors (*35*) studied 91 pairs of twins from the Swedish Twin Registry of 1967. The twins ranged in age from 42 to 67 years, and 51 pairs were monozygotic. Smoking habits were not significantly different in pairs discordant for the probable presence of CHD. However, Liljefors noted that "... in many pairs the smoking habits were similar and that the material included few pairs discordant with respect to smoking, so that it does not provide a suitable basis for conclusions as to the causal importance of smoking for CHD." As observed in the 1971 report, "The Health Consequences of Smoking" (*56*), it would be surprising if genetic factors did not play a role in heart disease; however, it is open to question whether findings from twin studies can be used to distinguish between "... the hypothesis that genetic factors govern the level of host susceptibility or resistance to the effects of an exogenous influence such as cigarette smoking and the hypothesis that genetic factors 'cause' both heart disease and smoking."

(*45*) STAMLER, J. Acute myocardial infarction—progress in primary prevention. British Heart Journal 33(Supplement): 145–164, 1971.

(*21*) GROSS, W., BIALEK, R., SCHADE, G., JUCHEMS, R. Serumlipid-Veränderungen beim Rauchen. (Serum lipid changes in smoking.) Deutsches Medizinisches Journal 21(6): 368–374, March 20, 1970.

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(*34*) LEREN, P. The Oslo diet-heart study. Eleven-year report. Circulation 42(5): 935–942, November 1970.

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(*35*) LILJEFORS, I. Coronary Heart Disease in Male Twins. Hereditary and Environmental Factors in Concordant and Discordant Pairs. Acta Medica Scandinavica (Supplementum 511), 1970. 90 pp.

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Prognosis of Myocardial Infarction. The details of (34) Leren's investigation are not recounted. The results do not show that smoking is related to mortality rate. The details are as follows:

Smoking Habits

Smoking habits were about the same in the two groups at entry and showed practically no change during the first 5 years of the trial. Because of the frequent combination of self-rolled cigarettes and a pipe, it was impossible to consider cigarette smokers alone. Table 10 presents the overall CHD mortality rate in relation to smoking habits. The death rate in the smokers tends to be higher than in the nonsmokers. However, the difference is small and not statistically significant. The incidence of sudden death was the same (20.3 and 20.5%) in smokers and nonsmokers. Smoking was not related to the serum cholesterol level.

Combined Risk Factors

Figure 5 evaluates the importance of an elevated serum cholesterol level as a risk factor in the presence of hypertension in smokers. The CHD mortality rate was three

Table 10

Eleven-Year Incidence of CHD Deaths in Relation to Smoking Habits: Both Groups Combined

	Nonsmokers	Smokers
At risk	146	266
Age (yr)	57.1	55.8
Cholesterol (mg 100 ml)	271	268
CHD deaths	54	119
%	37.0	44.7

times higher in the hypertensive smokers wi a cholesterol level above 250 compared wi normotensive nonsmokers with a cholester level below 250. This difference is high significant ($P = 0.007$).

Epidemiologic studies have demonstrated several factors associated with the risk of developing first manifestations of coronary heart disease. Blood lipids, blood pressure, and cigarette smoking are such risk variables. The present study demonstrates that these factors, all amenable to control, are of prognostic significance even after a myocardial infarction. When combining data from both groups, a three-fold greater CHD mortality rate is demonstrable among the hypercholesterolemic, hypertensive smokers than among those in whom these factors were low or absent. In spite of the small numbers this observation lends some support to the view that the multifactorial approach is the best way to the solution of the coronary heart disease problem.

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AUTOPSY STUDIES

In previously reported autopsy studies, Auerbach, et al. found that aortic and coronary atherosclerosis in man were more common and severe among smokers than among nonsmokers (*5*). They have now extended their investigations to the myocardial arterioles of men and beagle dogs (*6*). In a study of 1,184 men, they found that the thickness of myocardial arteriole walls was greater, on the average, in smokers than nonsmokers (table 3). The thickness increased with the number of cigarettes smoked per day and with age. The thickness was less, on the average, among cigar and pipe smokers than among cigarette smokers, but it was greater than in men who had never smoked regularly.

TABLE 3.—*Human autopsy study. Comparison of the thickness of myocardial arteriole walls in smokers and nonsmokers.*[1]

Age (years)	Smoking	Number of Men					Percent of Men		
		Total	‡Grade 0	‡Grade 1	‡Grade 2, 3	Total	‡Grade 0	‡Grade 1	‡Grade 2,3
<45	None	22	2	19	1	100.0	9.1	85.4	4.5
	Cigar, pipe	4	—	1	3	100.0	—	†25.0	†75.0
	Cig. 1–19	50	1	31	18	100.0	2.0	62.0	36.0
	Cig. 20–39	85	4	35	46	100.0	4.7	41.2	54.1
	Cig. ≥40	29	—	10	19	100.0	—	34.5	65.5
45–59	None	15	1	12	2	100.0	6.7	80.0	13.3
	Cigar, pipe	13	—	8	5	100.0	—	61.5	38.5
	Cig. 1–19	33	—	17	16	100.0	—	51.5	48.5
	Cig. 20–39	99	—	35	64	100.0	—	35.4	64.6
	Cig. ≥40	50	—	11	39	100.0	—	22.0	78.0
60–69	None	56	4	36	16	100.0	7.1	64.3	28.6
	Cigar, pipe	35	—	22	13	100.0	—	62.9	37.1
	Cig. 1–19	92	—	44	48	100.0	—	47.8	52.2
	Cig. 20–39	193	—	58	135	100.0	—	30.1	69.9
	Cig. ≥40	87	—	21	66	100.0	—	24.1	75.9
≥70	None	32	2	18	12	100.0	6.3	56.2	37.5
	Cigar, pipe	40	—	19	21	100.0	—	47.5	52.5
	Cig. 1–19	30	—	12	18	100.0	—	40.0	60.0
	Cig. 20–39	46	—	12	34	100.0	—	26.1	73.9
	Cig. ≥40	9	—	3	6	100.0	—	†33.3	†66.7

[1] In the right ventricular wall of 1,723 men by age and smoking habits.
† Percentages based on less than ten cases.
‡ Four Point Scale for the Thickness of Myocardial Arteriole Walls:
0—normal thickness; 1—slight thickness; 2—moderate thickness; 3—great thickness.

SOURCE: Auerbach, O., et al. (*6*).

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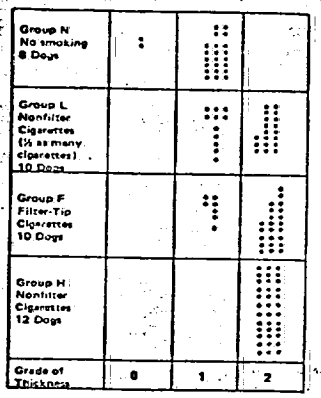
In one experiment, beagle dogs inhaled cigarette smoke daily through tracheostomae. Twenty-eight dogs that died between days 67 and 875 formed one group; 32 dogs that were killed after 875 days formed another group. Eight control dogs were not exposed. Beagle myocardial arteriole walls were found to be thicker in smoking than nonsmoking dogs, in dogs smoking many cigarettes than in dogs smoking fewer cigarettes, and in dogs smoking nonfilter cigarettes than in dogs smoking filter-tip cigarettes (figure 1). Also, the thickness of arteriole walls increased with the duration of smoking.



Each dot represents one section. The three dots on a line represent the three sections from a particular dog.

FIGURE 1.—Canine autopsy study. Comparison of the thickness of myocardial arteriole walls in 32 smoking dogs killed after 875 days and 8 nonsmoking dogs.

SOURCE: Auerbach, O., et al. (6).

EXPERIMENTAL STUDIES

NICOTINE AND CIGARETTE SMOKE

Schievelbein, et al. (47) investigated the effect of oral nicotine administration over a 20-month period on lipid metabolism in 35 rabbits. Even though lipoprotein lipase levels and calcium content of the aorta were significantly greater in the group given nicotine than in the control group, the histological changes of arteriosclerosis were found with equal frequency in both groups. The authors concluded that the epidemiological correlations between CHD and cigarette smoking could not be explained by the pharmacologic effect of nicotine alone.

A study of the interaction of chronic nicotine administration and acute hypoxia in 280 rats was performed by Wenzel and Richards (60). Pretreatment of the rats with nicotine increased the mortality during hypoxia, but the difference was not statistically significant. Pretreatment with the nicotine also was associated with marked variability of regression of hypoxic heart lesions. The interaction of nicotine pretreatment and the hypoxic insult produced variable effects on myocardial enzymes.

Aronow (1) recently studied the effect of cigarette smoking on the A wave of the apexcardiogram in 20 men with CHD. The A wave reflects the left ventricular filling wave associated with the impact of blood upon the ventricular wall during left atrial contraction. He found that the mean maximum increase in A wave ratio after smoking was 34 percent for high-nicotine cigarettes, 13 percent for the low-nicotine cigarettes, and 6 percent for the non-nicotine cigarettes. He ascribed these changes to increased myocardial ischemia produced by cigarette smoking, which was reflected by a larger A wave ratio in the apexcardiogram. While nicotine appears to have produced most of these changes, the observation that a 6 percent increase occurred in the absence of nicotine suggests the possibility that carbon monoxide plays a role in this effect.

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Histological Evidence of Atherosclerosis. The technique of measuring thickness of the wall only unrelated to the size of the lumen has been severely criticized. The accepted technique is wall to lumen ratio. Anyway, in the Discussion (6) Auerbach et al. recognize the problem relating to the cause of the thickness. If some measurements were taken prior to sacrificing the animals, the possibilities enumerated could have been explored. Furthermore, in the absence of functional measurements, it is impossible to detect ischemia.

It would be important to determine what ingredients of cigarette smoke are responsible for the greater thickness of walls of arterioles in smoking dogs than in dogs not exposed to cigarette smoke. As described above, the thickness was less on the average, in dogs that smoked filter-tip cigarettes than in dogs that smoked nonfilter cigarettes. The cellulose acetate filter used in this experiment resulted in a reduction of both tar and nicotine. This suggests that tar or nicotine or a combination of the two is responsible for the effects of smoking upon the thickness of walls of arterioles in the myocardium. However, in light of the findings of Harkavy[4] and the findings of Wanstrup, Kjeldsen, and Astrup[5] in experiments carried out on rabbits, we cannot rule out the possibility that allergy to tobacco proteins or that CO in cigarette smoke may have contributed to the observed effect of cigarette smoking upon the thickness of walls of arterioles in the myocardium of the beagle dogs.

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Carbon Monoxide

Because cigarette smoke contains from 2.7 to 6 percent carbon monoxide (CO), significantly higher carboxyhemoglobin (COHb) levels are found in smokers than nonsmokers (4, 20, 34, 62). COHb levels in nonsmokers are usually less than 1 percent, while those in smokers average around 4 percent and may exceed 15 percent (4, 20, 56). Heavy smokers and those who inhale show the highest carboxyhemoglobin levels (20).

Haebisch (24) found that a smoker with a daily consumption of 35 to 40 cigarettes easily attains and maintains for hours an alveolar CO concentration of 50 p.p.m., which reaches or exceeds legally-established ambient air quality standards (14, 18, 23, 24).

Cohen, et al. (13) and Aronow, et al. (2) have shown that there is no significant difference in mean expired air carbon monoxide levels after patients have smoked tobacco or lettuce leaf cigarettes. Although pipe and cigar smokers in the United States are reported to have lower exposure to CO than cigarette smokers (20), CO intoxication has been reported in cigar smokers (25).

CO exerts its adverse effects on the cardiovascular system of smokers through one or more of the following mechanisms: (a) reduction of the amount of hemoglobin available for oxygen transport; (b) shift of the oxygen-hemoglobin dissociation curve to the left with consequent interference in oxygen release at the tissue level; and (c) induction of arterial hypoxemia. CO may interfere with the homeostatic mechanism by which 2,3-DPG controls the affinity of hemoglobin for oxygen (56). CO has also been implicated in experimental atherogenesis in animals (56).

Ayres, et al. (7) recently studied 41 patients during diagnostic cardiac catheterization, at which time they inhaled either 5 percent or .1 percent CO. Arterial and mixed venous oxygen tensions were decreased by administration of either concentration. In patients with CHD, coronary artery O_2 extraction decreased 7.9 percent after inhalation of .1 percent CO and 30.5 percent after inhalation of 5 percent CO. Some of the patients with CHD experienced changes in lactate and pyruvate metabolism indicative of inadequate myocardial oxygenation. The higher level of CO inhalation in this experiment is comparable to that experienced intermittently by cigarette smokers.

Brewer and his colleagues (11) investigated cigarette smoking as a cause of hypoxemia in residents of Leadville, Colorado, at an altitude of 3,100 meters. The arterial pO_2 of 8 smokers was significantly lower ($P < .05$) than that of 12 nonsmokers, but this was reversible upon cessation of smoking. They concluded that the adverse effect of cigarette smoking on O_2 transport may be especially pronounced at high altitude and may restrict an individual's ability to adapt to reduced O_2 tensions (11, 12).

Kjeldsen (31, 32) examined 933 industrial workers, about one-half of whom were tobacco workers. Fifty-nine cases of arteriosclerosis were documented by such clinical symptoms as angina pectoris and intermittent claudication or by a previous history of myocardial infarction. While 20.9 percent of the 934 "control" individuals were nonsmokers, only 2 (3.4 percent) of the 59 patients with arteriosclerosis were nonsmokers. A significantly higher percentage of diseased workers were heavy smokers and inhaled the smoke.

Cholesterol Content of Tobacco and Tobacco Smoke

Cholesterol glucoside has not previously been reported in tobacco, or in any other plant (10). Bolt and Clarke (10) investigated the sterolin and sterol fraction of flue-cured tobacco and found that cholesterol is one of the major components of the sterol fraction.

More recently, Grunwald, et al. (22) have confirmed that cholesterol accounts for 10 percent of the total sterol in cigarette tobacco. They also found that 8.6 percent of the total sterol content of cigarette smoke condensate was cholesterol. Thirteen percent of the cholesterol present in cigarette tobacco was transferred to the condensate.

The biological significance of these findings remains to be determined.

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(10) Bolt, A. J. N., Clarke, R. F. Cholesterol glucoside in tobacco. Phytochemistry 9(4): 819–822, April 1970.

(22) Grunwald, C., Davis, D. L., Rush, L. P. Cholesterol in cigarette smoke condensate. Journal of Agricultural and Food Chemistry 19(1): 128–133, January–February 1971.

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Atherosclerosis and Carbon Monoxide. The results of (31, 32) Kjeldsen should be compared with the negative results of Petrovská and Draková (1967 and 1971). They examined individuals who have been exposed to an environment of up to 1,000 ppm carbon monoxide and blood levels of 2 to 26% for 10.5 years. These individuals did not develop any early lesions of atherosclerosis.

PREROVSKÁ I and DRDKOVÁ S: Vliv chronickeho pusobeni kyslicniku uhelnateho na biochemicke zmeny v seru vzbledem k aterosklerose. (The effect of chronic exposure to carbon monoxide on biochemical changes in the blood with respect to atherosclerosis). Prac Lek 19: 1-4, 1967a.

PREROVSKÁ I and DRDKOVÁ S: Vliv chronickeho pusobeni prumyslovych skodlivin na exponovane pracovniky vzhledem k rozvoji aterosklerozy. (Influence of the chronic action of industrial anoxious agents on exposed workers in relation to the development of atherosclerosis). Cas Lek Cesk 106: 754-759, 1967b.

PREROVSKÁ I and DRDKOVÁ S: Der Einfluß der chronischen Einwirkung von Kohlenoxyd auf den klinischen Zustand und biochemische Veranderungen im Serum exponierter Personen in Hinsicht auf die vorzeitige Entwicklung der Atherosklerose. (Influence of chronic action of carbon monoxide on the clinical status of biochemical changes in the serum of exposed persons on development of atherosclerosis with influence to the premature). Int Arch Arbeitsmed 28: 175-188, 1971.

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COR PULMONALE (PULMONARY HEART DISEASE)

The relationship between cigarette smoking and chronic obstructive bronchopulmonary disease (COPD) with cor pulmonale was discussed in the 1968 Supplement to "The Health Consequences of Smoking" (*55*).

Although the extent of morbidity and mortality due to cor pulmonale and right heart failure is difficult to determine, COPD is often complicated by these conditions (*27*).

The Pulmonary Heart Disease Study Group of the Inter-Society Commission for Heart Disease Resources recently summarized the evidence linking cigarette smoking with COPD and concluded: "Cigarette smoking is the major cause of pulmonary heart disease in that it is the most important cause of the chronic non-neoplastic bronchopulmonary diseases in the United States" (*28*).

CEREBROVASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (*56*), summarized the data linking smoking to cerebrovascular disease as follows:

1. Data from numerous prospective studies indicate that cigarette smoking is associated with increased mortality from cerebrovascular disease.
2. Experimental evidence concerning the relationship of smoking and cerebrovascular disease is at present insufficient to allow for conclusions concerning pathogenesis. However, some of the pathophysiological considerations discussed concerning CHD may also pertain to the relationship of smoking and CVD, particularly cerebral infarction.

In the interim, additional reports have been published.

Dyken (*15*) performed a retrospective study on 285 patients with cerebrovascular disease in Elkhart, Indiana. Even though low cigarette consumption was noted in all groups, males who had cerebral infarctions smoked significantly more than controls.

Paffenbarger, et al. (*42*) found that smokers of more than 20 cigarettes a day faced a slightly increased but not significantly greater risk of dying from a stroke than those smoking lesser amounts.

After 16 years follow-up, male cigarette smokers in the Framingham study had more than three times the nonsmokers' risk of developing a cerebral infarction (*29*). However, Kannel commented: "It is not clear that smoking actually affects the rate of cerebral atherogenesis, and some other mechanism may be involved."

(15) DYKEN, M. L. Precipitating factors, prognosis, and demography of cerebrovascular disease in an Indiana community: A review of all patients hospitalized from 1963 to 1965 with neurological examination of survivors. Stroke 1(4): 261–269, July-August 1970.

(29) KANNEL, W. B. Current status of the epidemiology of brain infarction associated with occlusive arterial disease. Stroke 2(4): 295–318, July–August 1971.

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PERIPHERAL VASCULAR DISEASE

The 1971 report, "The Health Consequences of Smoking" (*56*), summarized the data relating smoking to peripheral vascular disease as follows:

1. Data from a number of retrospective studies have indicated that cigarette smoking is a likely risk factor in the development of peripheral vascular disease. Cigarette smoking also appears to be a factor in the aggravation of peripheral vascular disease.

2. Cigarette smoking has been observed to alter peripheral blood flow and peripheral vascular resistance.

Newly published studies add to our understanding of the effect of nicotine or tobacco smoke on the peripheral circulation and of the significance of smoking in peripheral vessel atherogenesis.

Martz, et al. (*37*) observed that some of the apparently conflicting data on the effects of nicotine upon the peripheral vasculature may result from interpretations based upon indirect measurements of microcirculatory variables. Hence, they studied vascular changes in a bat wing under direct microscopic observation. They noted a marked increase in the diameter of innervated, minute arteries with intraperitoneal nicotine administration, but this effect was abolished with sympathetic denervation.

Asano and Branemark (*3*) installed a direct, microscopic observation chamber in the connective tissue of two human volunteers. One volunteer was a "healthy" 20-year-old male nonsmoker. The other volunteer was a diabetic who had been a smoker for five years and who "...had no apparent diabetic vasculopathy." The effects of tobacco smoking on the microcirculation of these volunteers included: "...vasoconstriction, decrease in blood flow rate and frequency of plasma spacing, blocking of blood flow in varying numbers of nutritive capillaries, shunting of blood from arterioles to venules...." These microcirculatory changes were said to result in a decrease of nutritive blood flow in tissue.

As mentioned in the discussion of CHD, Kjeldsen (*31, 32*) studied several smoking patients with occlusive peripheral vascular disease whose COHb levels were significantly higher than those of control smokers. The levels of COHb in many of these patients were comparable to those associated with experimental atherosclerosis in animals. Astrup, et al. (*4*) have suggested that prospective studies should be performed to investigate the relationship between COHb levels and the incidence of arterial disease.

In the Prague study (*19*) intermittent claudication was significantly ($P < .01$) more common among cigarette smokers than nonsmokers. Twenty percent of the men in the age group of 60 to 64 who were heavy smokers (more than 25 cigarettes a day) had intermittent claudication.

Räf (*44*) reported that all but 4 of the 98 patients admitted for peripheral vascular surgery at the Karoline Hospital, Sweden, were smokers.

Mathiesen, et al. (*38*) in Denmark followed the spontaneous course of arterial insufficiency in 211 patients. Cessation of smoking increased the number of patients displaying spontaneous improvement.

ORAL CONTRACEPTIVES, THROMBOPHLEBITIS, AND SMOKING

In two studies from Great Britain and one from the United States, it was reported that the use of oral contraceptives was associated with a significantly increased risk of developing venous thromboembolism (*46, 58, 59*). The British investigators also noted in their initial report that the affected patients were, on the average, heavier smokers than controls (*58*). However, after an additional year of study, a similar effect was not noted and they concluded (*59*): "...the earlier difference between the smoking habits of the two groups can thus reasonably be attributed to chance ($P = 0.08$)." The American investigator (*45*) found "...no evidence that smoking, acting either independently or in conjunction with oral contraceptives, is a factor in idiopathic thromboembolism."

Cigarette smoking has not been clearly demonstrated to be a factor that contributes to the risk of idiopathic thromboembolism associated with the use of oral contraceptives. Nevertheless, the possibility that it may act to increase that risk has not yet been completely ruled out.

(37) Martz, R. C., Youkilis, E. J., Harris, P. D., Forney, R. B., Nicoll, P. A. Effects of nicotine on the subcutaneous microcirculation of the bat. Proceedings of the Society for Experimental Biology and Medicine 133(1): 153–159, January 1970.

(3) Asano, M., Branemark, P.-I. Cardiovascular and microvascular responses to smoking in man. Advances in Microcirculation 3: 125–153, 1970.

(44) Räf, L. E. Medicinska skadeverkningar av rökning. Rökning och perifera kärlsjukdomar. (Harmful clinical effects of smoking. Smoking and diseases of the peripheral vessels.) Social-Medicinsk Tidskrift 2 (Special No.): 67–71, February 1971.

(38) Mathiesen, F. R., Larsen, E. E., Wulff, M. Some factors influencing the spontaneous course of arterial vascular insufficiency. Acta Chirurgica Scandinavica 136(4): 303–308, 1970.

(46) Sartwell, P. E., Masi, A. T., Arthes, F. G., Greene, G. R., Smith, H. E. Thromboembolism and oral contraceptives: An epidemiologic case-control study. American Journal of Epidemiology 90(5): 365–380, November 1969.

(58) Vessey, M. P., Doll, R. Investigation of relation between use of oral contraceptives and thromboembolic disease. British Medical Journal 2: 199–205, April 27, 1968.

(59) Vessey, M. P., Doll., R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. British Medical Journal 2(5558): 651–657, June 14, 1969.

(45) Sartwell, P.E. Oral contraceptives and thromboembolism: A further report. American Journal of Epidemiology 94(3): 192–201, September 1971.

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HIGHLIGHTS OF CURRENT CARDIOVASCULAR INFORMATION

In addition to the comprehensive summary from the 1971 report, "The Health Consequences of Smoking" (*56*), cited earlier in this chapter, the following statements are made to emphasize the most recent developments in the field:

1. Recent epidemiological studies from several countries confirm that cigarette smoking is one of the major risk factors contributing to the development of CHD. Avoidance of cigarette smoking is of importance in the primary prevention of CHD.
2. Studies in man and animals have shown a greater myocardial arteriole wall thickness in smokers than nonsmokers.
3. Experimental and epidemiological investigations implicate the elevation of carboxyhemoglobin levels in smokers as a contributor to the development of CHD and arteriosclerotic peripheral vascular disease.
4. Cigarette smoking is considered to be the major cause of pulmonary heart disease (cor pulmonale) in the United States in that it is the most important cause of chronic nonneoplastic bronchopulmonary diseases. Avoidance of cigarette smoking is of importance in the primary prevention of pulmonary heart disease.

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Cigarette Consumption. In 1971, Seltzer wrote a letter to the Editor (N Engl J Med 11 March, 1971) commenting on the secular rise in death rate from heart disease paralleling the secular increase in cigarette consumption. This topic has been omitted from the 1972 Document. The response of Grannis (N Engl J Med 284: 1384-1385, 1971) is also reproduced.

CIGARETTES AND HEART DISEASE

To the Editor: It has been suggested that the secular rise in death rate from heart disease parallels the secular increase in cigarette consumption. In this connection, the recently published World Health Organization's data on the death rates from arteriosclerotic and degenerative heart disease for the age group 45 to 54 and for the years 1955 to 1967 are most interesting.

Table 1 gives in rank order the percentage changes in adult per capita cigarette consumption and the appropriate

Table 1. Death Rates from Arteriosclerotic Heart Disease in Relation to Smoking.

Country	Cigarette Consumption/Adult*	Death Rate from Arteriosclerotic Heart Disease
	Changes in % (1967/1955)	Changes in % (1967/1955)
Finland†	− 5	+30
UK	+ 13	+29
Netherlands	+ 17	+53
US	+ 18	+ 1
France‡	+ 33	+39
Switzerland	+ 38	+10
Sweden‡	+ 39	+10
Italy	+ 46	+13
Canada‡	+ 47	+ 8
Japan‡	+ 48	−27
Australia	+ 51	+28
Austria‡	+ 55	+32
W. Germany‡	+200	+20

*Tobacco Consumption in Various Countries. Second edition. Edited by DH Bone. London, Tobacco Research Council (Research Paper 6), 1968

†Lawrence J: The modern epidemic: ischaemic heart disease. World Health, August-September, 1970, pp 3-11

‡Based on 1966 cigarette & death-rate figures from arteriosclerotic heart disease since 1967 tobacco figures have not been available.

death rates from arteriosclerotic heart disease for the countries listed by WHO from 1955 to 1967. From this table, it appears that there is no rank-order association between cigarette consumption and death rates from arteriosclerotic heart disease. In fact, among the five countries with the smallest changes in cigarette consumption, four countries (Finland, United Kingdom, Netherlands and France) show the largest percentage increases in heart-disease mortality. Striking is Finland which plays a 5 per cent decrease in per capita cigarette consumption, and yet over the same period has experienced a 30 per cent increase in deaths from arteriosclerotic heart disease.

Of further interest is the fact that whereas Japan has had a 48 per cent increase in cigarette consumption, its death rate from arteriosclerotic heart disease over the same period has declined 27 per cent. West Germany, with a 200 per cent increase in cigarette consumption, shows only a 20 per cent increase in arteriosclerotic heart disease. For the United States the death rate from this cause is essentially unchanged, whereas our country has experienced an 18 per cent rise in per capita consumption. These data do not support the parallelism of secular changes in cigarette consumption and heart-disease mortality.

I do not draw any conclusions regarding the effect of cigarette smoking on heart-disease mortality from these figures, except to point out the danger of the use of secular changes in tobacco consumption and heart-disease mortality for this purpose. Obviously, the etiology of heart disease is far too complex for such simplistic interpretations from these kinds of statistical data.

CARL C. SELTZER, PH.D.
Senior Research Associate in Biological Anthropology
Harvard School of Public Health

To the Editor: C. C. Seltzer, of the Harvard School of Public Health, recently tabulated data purporting to show a poor correlation of secular changes in cigarette consumption with heart disease mortality rates (N Engl J Med 284:1357, 1971). However, the kind of statistics used (percentage changes rather than absolute changes, and combined death rates of males and females rather than death rates of males) were inappropriate for evaluating this non-controversial, secure-fact correlation. Figure 1 puts these data in a clearer perspective.

Seltzer emphasized apparent inconsistencies such as the disproportionate changes in the Netherlands and England as compared to changes in countries such as West Germany and Canada. Figure 1 shows that the changes observed in these and many other countries were in fact in good agreement with the relation previously established in epidemiologic studies.

The purpose of Seltzer's communication may have been to point out, correctly, that factors other than cigarette smoking are important in the etiology of heart disease, particularly among nonsmokers and in countries such as Japan, France, Switzerland and especially Finland. However, the tenor of his presentation discounted the major role of cigarette smoking in causing premature mortality of males, par-

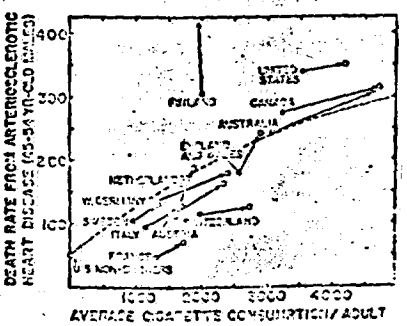

Figure 1. Average Cigarette Consumption per Adult per Year and Heart Disease Mortality (45 to 54 Year Old) Observed in Epidemiologic Studies of U.S. Men (●) and in Various Countries in 1955 (○) and 1967 (○). The arrows show the changes that occurred in each country. The 18 per cent increase in cigarette consumption in the United States during the 12 years shown in Figure 1 is artificial, being due to an increase in the amount of tobacco per cigarette, particularly from heart disease, and his choice of statistics confused an otherwise clear situation.

Thus, I conclude that secular changes in heart disease mortality rates have indeed paralleled changes in cigarette consumption, confirming on a worldwide basis that cigarette smoking continues to be a major health problem that merits the concerned attention of national leadership.

The problem of cigarette smoking is serious because of the large decrease in average longevity of smokers, the large number of smokers and the long period of involvement with smoking. The problem has been well documented at all levels of scientific inquiry, and serious socioeconomic disruptions of contemporary American society caused by smoking have been noted.[1,2,3] Nevertheless, national leadership has been unable to arrive at a meaningful solution to the problem, partly because of obfuscation of issues by specious statistical interpretations.

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THE HEALTH CONSEQUENCES OF SMOKING

JANUARY 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service

CHAPTER 1

CONTENTS

CARDIOVASCULAR DISEASES

Page

INTRODUCTION 3

CORONARY HEART DISEASE

Epidemiological Studies

Smoking and Certain Risk Factors 4

Blood Lipids 14

Electrocardiogram 16

Experimental Studies

Cigarette Smoke 17

Nicotine 20

Carbon Monoxide 24

Smoking and Thrombosis 26

CEREBROVASCULAR DISEASE 26

PERIPHERAL VASCULAR DISEASE 27

SUMMARY OF RECENT CARDIOVASCULAR FINDINGS 34

REFERENCES 35

Figure 1.--Age-adjusted incidence rates of CHD by body weight and cigarette smoking (white males) 6

Figure 2.--Age-adjusted incidence rates of CHD comparing farmers who smoke cigarettes with nonsmoking farmers 7

Figure 3.--Standardized mortality ratios for arteriosclerotic heart disease for males and females by age at initiation of cigarette smoking 9

Figure 4.--The effect of cigarette smoke inhalation on the ventricular fibrillation threshold of normal dogs and dogs with experimentally produced acute myocardial infarction 19

Figure 5.--Effects of smoking five consecutive cigarettes on plasma nicotine concentration 22

Figure 6.--Relative risk of developing arteriosclerosis obliterans for males by amount of cigarettes smoked 29

Figure 7.--Relative risk of developing arteriosclerosis obliterans for females by amount of cigarettes smoked 30

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CARDIOVASCULAR DISEASES

INTRODUCTION

In the United States, coronary heart disease (CHD) is the leading cause of death and is the largest contributor to excess deaths among cigarette smokers. The following is a brief summary of the major relationships between smoking and cardiovascular diseases as outlined in previous reports of the health consequences of smoking *(62, 63, 64, 65, 66, 67)*.

Many prospective and retrospective epidemiological studies have identified cigarette smoking, elevated serum cholesterol, and high blood pressure as major risk factors for the development of coronary heart disease. Cigarette smoking acts independently of and synergistically with the other CHD risk factors to greatly increase the risk of developing coronary heart disease. The risk of developing CHD for pipe and cigar smokers is much less than it is for cigarette smokers, but more than it is for nonsmokers. In the United States, cigarette smoking can be considered the major cause of cor pulmonale since it is the most important cause of chronic non-neoplastic bronchopulmonary disease.

Autopsy studies have demonstrated that aortic and coronary atherosclerosis are more common and severe, and myocardial arteriole wall thickness is greater, in cigarette smokers than in nonsmokers.

Those who stop smoking cigarettes experience a decreased risk of death from coronary heart disease compared to that of continuing smokers.

Experimental studies in humans and animals suggest that cigarette smoking may contribute to the development of CHD through the action of several independent or complementary mechanisms: the formation of significant levels of carboxyhemoglobin, the release of catecholamines, inadequate myocardial oxygenation which may result from a number of mechanisms, and an increase in platelet adhesiveness which may contribute to acute thrombus formation. There is evidence that cigarette smoking may accelerate the pathophysiological changes of preexisting coronary heart disease and therefore contributes to sudden death from CHD.

Recently published epidemiological, autopsy, and experimental investigations have added to the understanding of the association between smoking and cardiovascular diseases.

62. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoki A Public Health Service Review: 1967. U.S. Department of Health, Education, and Welfare. Washington, Public Health Service Publication No. 1696, Revised January 1969. 227 pp.

63. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking. 1968 Supplement to the 1967 Public Health Service Review. U.S Department of Health, Education, and Welfare. Washington, Public Health Service Publication 1696, 1968. 117 pp.

64. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoking 1969 Supplement to the 1967 Public Health Service Review. U.S. Department of Health, Education, and Welfare. Washingto Public Health Service Publication 1696-2, 1969. 98 pp.

65. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoki A Report of the Surgeon General: 1971. U.S. Department of Health, Education, and Welfare. Washington, DHEW Publicatio No. (HSM) 71-7513, 1971. 458 pp.

66. U.S. PUBLIC HEALTH SERVICE. The Health Consequences of Smoki A Report of the Surgeon General: 1972. U.S. Department of Health, Education, and Welfare. Washington, DHEW Publicatio No. (HSM) 72-6516, 1972. 158 pp.

67. U.S. PUBLIC HEALTH SERVICE. Smoking and Health. Report of the Advisory Committee to the Surgeon General of the Public Healt Service. Washington, U.S. Department of Health, Education, a Welfare, Public Health Service Publication No. 1103, 1964. 3

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CORONARY HEART DISEASE

Epidemiological Studies

Smoking and Certain Risk Factors

A prospective epidemiological study of the factors associated with cardiovascular diseases was conducted among the 4,847 white and 2,434 black men and women of Evans County, Georgia *(23)*. The investigation was initiated with a private census and preliminary examinations beginning in 1960. Follow-up examinations were conducted after seven years. Cassel *(13)* reported that high blood pressure, elevated serum cholesterol, and cigarette smoking were major risk factors for the development of coronary heart disease. Increased body weight, an elevated hematocrit, and ECG abnormalities were additional factors that were associated with elevated CHD rates. A significant finding of this study was the very low prevalence and incidence of coronary heart disease (myocardial infarction and angina pectoris) in black men. The age-adjusted prevalence rates among black men were only half those of white men. The study showed that blacks were affected by the various risk factors for CHD in a similar fashion to whites but at a lower level of disease. This appeared to be true for any level or any risk factor or any combination of risk factors. Greater physical activity of blacks as compared to whites appeared to account for part of the observed differences in rates.

In this study, subjects were classified on the basis of their smoking history at enrollment and both current smokers and ex-smokers were considered smokers. Both black and white male smokers had a higher incidence of CHD than did nonsmokers, but white males had a higher incidence than blacks whether they were smokers or not. The age-adjusted incidence rate for white nonsmokers was 52.7 per thousand compared to 9.8 per thousand for black nonsmokers. White smokers had an incidence of 101, whereas the rate in black smokers was only 32.5. The prevalence of CHD increased with the number of cigarettes smoked per day in both groups.

The combined effect of body weight and cigarette smoking on the incidence of CHD was also examined *(25)*. The "Quetelet index"[1] was used to determine relative weight. The risk of developing CHD did not change with increases in relative weight among nonsmokers, but smokers experienced a substantial risk of developing CHD with increases in weight (figure 1).

The relationship of smoking to occupation and CHD was examined *(14)*. Farmers who performed sustained physical activity had lower rates of CHD than nonfarmers. Figure 2 shows that, while smoking increased the risk of CHD in both farmers and nonfarmers, farmers had lower rates than nonfarmers whether or not they smoked.

[1] Quetelet index = $\frac{\text{weight}}{\text{height}^2} \times 100$

23. HAMES, C. G. Introduction. (Evans County Cardiovascular and Cerebrovascular Epidemiologic Study.) Archives of Internal Medi 128(6): 883-886, December 1971.

13. CASSEL, J. C. Summary of major findings of the Evans County cardiovascular studies. Archives of Internal Medicine 128(6 887-889, December 1971.

26. HEYDEN, S., CASSEL, J. C., BARTEL, A., TYROLER, H. A., HAMES, CORNONI, J. C. Body weight and cigarette smoking as risk f Archives of Internal Medicine 128(6): 915-919, December 197

14. CASSEL, J. C., HEYDEN, S., BARTEL, A. G., KAPLAN, B. H., TYROLER, H. A., CORNONI, J. C., HAMES, C. G. Occupation and physical activity and coronary heart disease. Archives of Internal Medi 128(6): 920-926, December 1971.

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Occupation and Smoking. This paragraph implies that smoking is a more important risk factor than physical activity. The cited reference (14) Cassel et al. summarizes the epidemiologic investigation on the importance of physical activity in determining the incidence of coronary heart disease. The authors concluded that the differences in proportion of smokers was not sufficient to account for the prevalence of coronary heart disease.

In contrast to these biological risk factors, there were sizable differences in the proportion smoking cigarettes, with fewer farmers smoking at each age than nonfarmers (Table 3). Accordingly, before concluding that the difference in incidence between farmers and nonfarmers was due to the physical activity involved in farming, the effect of cigarette smoking in farmers and nonfarmers had to be examined.

From Table 4 and Fig 2 it can be seen that, while smoking increased the risk of CHD in both farmers and nonfarmers, farmers had lower rates than nonfarmers whether they smoked or not. The lower rates in farmers must, therefore, be due to some factors other than cigarette smoking.

Table 4.—Incidence of CHD* (1950-1962 to 1957-1969) in White Men, Farmers and Nonfarmers, by Age and Cigarette Smoking Status

1960 Cigarette Smoking	1960 Age, Yr	Farmers (1950 Occupation)			Nonfarmers (1960 Occupation)		
		No.	Cases	Rate	No.	Cases	Rate
Smokers and exsmokers	40-44	16	0	...	46	5	104
	45-54	59	4	68	122	11	90
	55-64	35	3	85	52	13	250
	65-74	11	4	364	33	8	242
	75+	2	0	...	3	2	667
	All ages	125	11	88	258	39	157
	Age-adjusted rate			93.7			158.2
Nonsmokers	40-44	12	0	...	13	0	...
	45-54	32	1	31	35	3	86
	55-64	40	3	75	27	1	37
	65-74	32	4	125	14	5	357
	75+	0	0	...	1	0	...
	All ages	116	8	69	90	9	100.0
	Age-adjusted rate			59.6			96.3
Unknown	40-44	7	0	...	11	4	364
	45-54	0	0	...	1	0	...
	55-64	1	0	...	0	0	...
	65-74	0	0	...	0	0	...
	75+	0	0	...	0	0	...
	All ages	8	0	...	12	4	333
	Age-adjusted rate			0			478

* Coronary heart disease.

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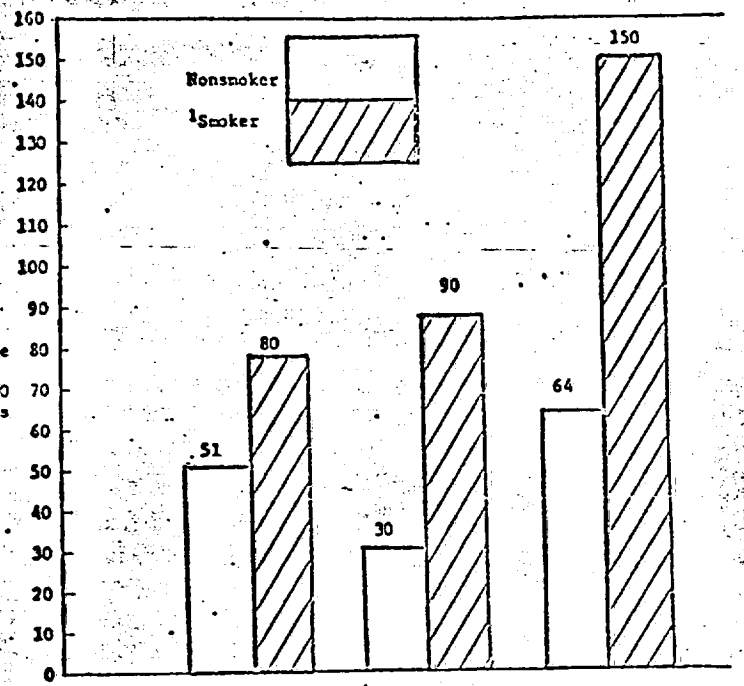

[3]Distribution by weight	Lower third (lean)		Middle third		Upper third (obese)	
Number	90	183	99	161	127	119
Cases	5	15	3	14	16	9

[1]Smokers excluding ex-smokers.
[2]87 months follow-up period.
[3]Based on Quetelet index.

Figure 1.--Age-adjusted incidence rates of CHD by [3]body weight and [1]cigarette smoking (white males).

SOURCE: Heyden, S., et al. *(26)*.

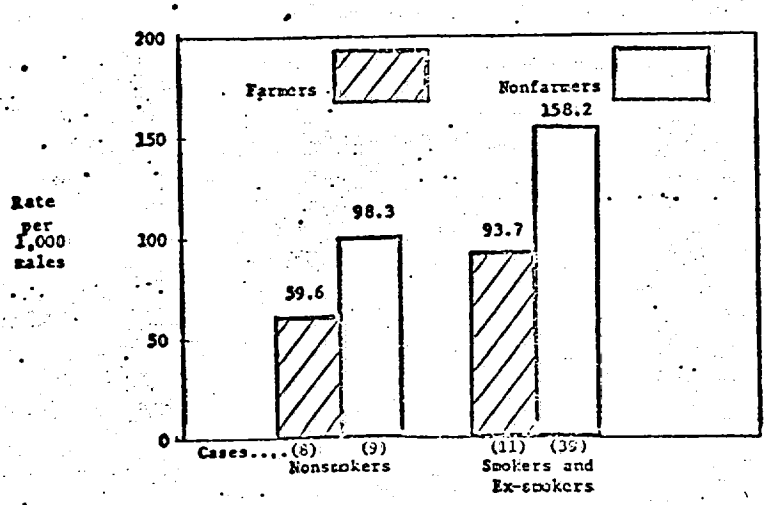

Figure 2.--Age-adjusted incidence rates of CHD comparing farmers who smoke cigarettes with nonsmoking farmers.

SOURCE: Cassel, J. C., et al. *(14)*.

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Hirayama (27) reported 5-year follow-up data on smoking in relation to death rates from a large prospective epidemiological study of 265,118 men and women in Japan. This investigation was the first of its kind to be conducted in an Asian population. During the follow-up period, 11,058 deaths occurred during 1,269,392 person years of observation. Male and female cigarette smokers experienced higher mortality rates from arteriosclerotic heart disease than did nonsmokers. Among cigarette smokers, the mortality ratios for arteriosclerotic heart disease were 1.56 ($P < .001$) for men and 1.44 ($P < .05$) for women. Dose-response relationships were found for both men and women as measured by the number of cigarettes smoked per day and age at initiation of smoking (figure 3).

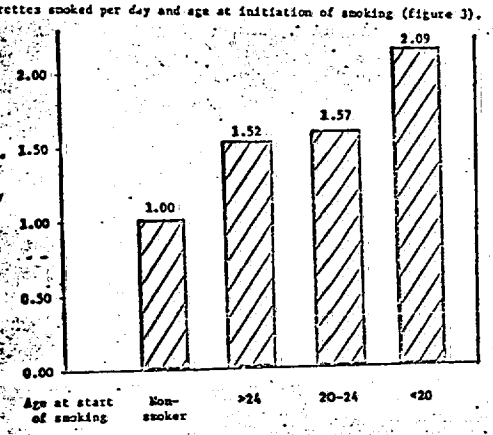

Figure 3.—Standardized mortality ratios for arteriosclerotic heart disease for males and females by age at initiation of cigarette smoking (Prospective study 1966-1970).

SOURCE: Hirayama, T. (27).

Gordon, et al. (22, 57), in a further analysis of the Framingham data, considered both by univariate and multivariate analysis the relation of certain key characteristics to the development of coronary heart disease. The characteristics were: high blood pressure, elevated serum cholesterol, cigarette smoking, left ventricular hypertrophy diagnosed by electrocardiogram, and glucose intolerance. Cigarette smoking emerged as one of the important risk factors for the development of coronary heart disease. There was a strong association between cigarette smoking and CHD other than angina pectoris, particularly among young male and female smokers. The relative role of cigarette smoking as a risk factor was emphasized by multivariate analysis. Cigarette smoking was not as strongly related to CHD in women as it was in men. This may have been in part due to the fact that there are fewer heavy smokers among women, and women tend to inhale smoke less than men.

HIRAYAMA, T. Smoking in relation to the death rates of 265,... men and women in Japan. A report of five years of follow-... Presented at the American Cancer Society's Fourteenth Scie... Writers' Seminar, Clearwater Beach, Florida, March 27, 197... 15 pp.

22. GORDON, T., SORLIE, P., KANNEL, W. B. Section 24. Coronary heart disease, atherothrombotic brain infarction, intermittent claudication—a multivariate analysis of some factors related to their incidence: The Framingham Study, 16-year follow-up. IN: Kannel, W. B., Gordon, T. (Editors). The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. May 1971. 42 pp.

57. SHURTLEFF, D. Section 26. Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study, 16-year follow-up. IN: Kannel, W. B., Gordon, T. (Editors). The Framingham Study. An Epidemiological Investigation of Cardiovascular Disease. U.S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, Washington, D. C., December 1970. 35 pp.

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Kagan, et al. *(31)* reported preliminary findings from the Honolulu Heart Study. The effect of migration on dietary patterns and the incidence of cardiovascular diseases in a cohort of men of Japanese ancestry born between 1900 and 1919, who were residents of Oahu in 1965, was examined in this prospective study. During the two years of follow-up, 101 men developed CHD in the population of 8,006 men initially examined. A significant relationship to CHD was found for the following risk factors: cigarette smoking, elevated systolic and diastolic blood pressure, increased serum cholesterol, triglycerides or uric acid, and various measures of obesity.

Using data from the International Cooperative Study on Cardiovascular Epidemiology, Keys, et al. *(34)* calculated the probabilities for men aged 40 to 59 to develop coronary heart disease in five years. The authors noted "...that the relative CHD risk of different men within a given population is well predicted from the results of the multivariate analysis of the experience of men in other far-distant populations differing in socioeconomic circumstances, language, and ethnic background." Although the CHD incidence rate of European men was about half that of the Americans, the fact still remained that investigation of the four variables (cigarette smoking, age, systolic blood pressure, and cholesterol) was sufficient to identify men whose likelihood of dying of CHD or having a definite myocardial infarction within five years was greatly above the average.

Punsar *(51)* reported 10-year follow-up data on the cohort of men in Finland who were part of the 7-country study of coronary heart disease, confirming that cigarette smoking was a major risk factor for CHD. The authors reported a 1.7-fold increase in CHD mortality among cigarette smokers. They estimated that 1,700 excess CHD deaths occur each year among cigarette smoking men in Finland.

Kozarevic, et al. *(38)* reported the results of the initial prevalence survey and the 2-year incidence data from the Yugoslavian study of cardiovascular disease. A total of 11,121 men between the ages of 35 and 62 were examined in the towns of Tuzla and Remetinec. Criteria for the diagnosis of CHD were based on objective electrocardiographic findings of myocardial infarction, left bundle branch block, or sudden death. A very low prevalence of myocardial infarction was initially found, and only 36 new cases of CHD developed over the 2-year period. The subjects who developed CHD smoked cigarettes at about the same level as the total study population. The annual average incidence rate of acute coronary heart disease was about 1.6 per 1,000 among both the smokers and nonsmokers. The CHD incidence rates found in this Yugoslavian study are appreciably below those found in the United States.

Comstock *(16)* examined the association between water hardness, various other environmental factors including cigarette smoking, and death from CHD. A total of 189 deaths from CHD occurred in the population of Washington County, Maryland, in the 3-year period following a census in 1963. For each case, two controls were randomly selected from the census lists and matched for race, sex, and year of birth. The relative risk of CHD for all smokers was 1.3 compared to nonsmokers ($P < .05$). This relative risk among cigarette smokers was dose-related; persons smoking more than two packs a day had the highest risk of CHD.

31. KAGAN, A., RHOADS, G. G., ZEEGEN, P. D., NICHAMAN, M. Z. Coronary heart disease among men of Japanese ancestry in Hawaii. The Honolulu Heart Study. Israel Journal of Medical Sciences 7(12): 1573-1577, December 1971.

34. KEYS, A., ARAVANIS, C., BLACKBURN, H., VAN BUCHEM, F. S. P., BUZINA, R., DJORDJEVIC, B. S., FIDANZA, F., KARVONEN, M. J., MENOTTI, A., PUDDU, V., TAYLOR, H. L. Probability of middle-aged men developing coronary heart disease in five years. Circulation 45(4): 815-[illegible] April 1972.

51. PUNSAR, S. Tupakointi ja sepelvaltiotauti. (Cigarette smoking and coronary heart disease.) Suomen Lääkärilehti 26(1/2): 27-32, January 9, 1971.

38. KOZAREVIC, D., PERC, B., DANDEN, T. R., KANN, H. A., ZUKEL, W. J. Prevalence and incidence of coronary disease in a population study. The Yugoslavia Cardiovascular Disease Study. Journal of Chronic Diseases 24(7/8): 495-505, September 1971.

16. COMSTOCK, G. W. Fatal arteriosclerotic heart disease, water hardness at home, and socioeconomic characteristics. American Journal of Epidemiology 94(1): 1-10, July 1971.

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Environmental Factors . The epidemiologic studies cited in this page are not described completely. For example, (16) Comstock reported other factors which influence the risk of coronary heart disease. Deaths from heart disease were more common among persons of lower socioeconomic status and among persons who attended church infrequently. As a matter of fact, the correlation with church attendance was better that with cigarette smoking. The illustration on risk factors, Comment and Summary are as follows:

Comstock, G. W. (Training Center for Public Health Research, Johns Hopkins School of Hygiene and Public Health, Box 2067, Hagerstown, Md. 21740). Fatal arteriosclerotic heart disease, water hardness at home, and socioeconomic characteristics. *Amer J Epidem* 94: 1–10, 1971.—Several reports have indicated an inverse correlation between the hardness of community water supplies and deaths from arteriosclerotic and degenerative heart disease. An unusual opportunity to look at this association in more detail arose in Washington County, Maryland. Drinking water sources there vary markedly in hardness, and a private census in 1963 made it possible to match cases and controls from the same defined population and to study a number of socioeconomic characteristics. During the next three years, there were 189 deaths attributed to arteriosclerotic and degenerative heart disease among white males aged 45 to 64 who could be identified in the census. For each case, 2 controls were randomly selected from the census lists and matched for race, sex and year of birth. Water samples were collected from the residences of cases and controls and examined for total hardness. No significant association of arteriosclerotic and degenerative heart disease deaths could be found with water hardness. Deaths from these causes were more common among persons of lower socioeconomic status, among cigarette smokers, and among persons who attended church infrequently. Although water hardness is not likely to be a real risk factor for cardiovascular disease, the role of trace elements in home drinking water supplies should be investigated.

arteriosclerosis; coronary disease; epidemiology; heart diseases; religion; water

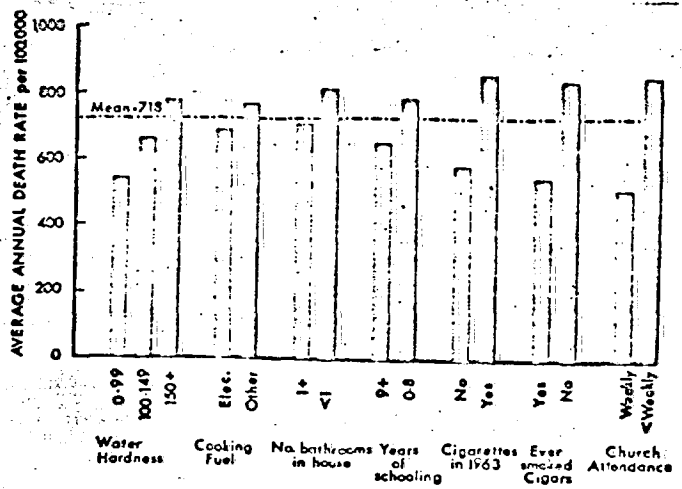

FIGURE 1. Average annual death rates from ASDHD for white males, 45–64 years, Washington County, Maryland, by hardness of home drinking water and selected socioeconomic and personal characteristics. (Each rate adjusted for all other selected characteristics and for age.)

A surprising finding was the strong negative association of frequency of religious attendance with fatal arteriosclerotic heart disease. It is premature to speculate on the meaning of this association other than to note that it is obvious that regular church attenders differ in many ways from those who rarely or never go to church. It is also possible that church attendance may produce a favorable psychic or emotional response. Because frequency of attendance is an aspect of religious experience that is very easily determined, it is hoped that future investigations will include information on church attendance to confirm or deny its importance as a risk factor for arteriosclerotic heart disease. If confirmed, the implications of this finding raise intriguing questions for future research.

The implications of identifying a water factor in the causation of arteriosclerotic cardiovascular disease are quite different. If some component of drinking water is causing disease, it can almost certainly be reduced or removed. If the water factor is a deficiency of some kind, this can be remedied. In either case, preventive treatment could quickly benefit large segments of the population. It is this possibility of an effective mass attack on a major health problem that makes further exploration for a water factor a matter of high priority.

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Casciu, et al. *(12)* reported the prevalence of cardiovascular diseases among 4,668 miners on Sardinia. Smoking and drinking habits, blood pressure, and heart rates were recorded. Smokers had higher rates of CHD than nonsmokers, and a dose-response was noted with the number of cigarettes smoked per day. The prevalence of myocardial infarction was 0.9 percent for nonsmokers, 1.62 percent for smokers of 10 or less cigarettes, 2.34 percent for smokers of 11 to 20 cigarettes, 6.8 percent for smokers of 20 or more cigarettes a day, and 1.42 percent for cigar or pipe smokers. When cigarette smokers were grouped by alcohol consumption, no significant difference was found in the prevalence of myocardial infarction between drinkers and nondrinkers.

Kornitzer, et al. *(35, 36, 37)* examined the prevalence of CHD in 566 male bank employees aged 40 to 59 in Brussels. They determined an individual's smoking history, blood lipids, ECG, peak flow rates, relative weight, skinfold thickness, and blood pressure. The prevalence of possible CHD as determined by ECG and CHD history was 7.1 percent in nonsmokers, 11.6 percent in cigarette smokers who inhaled, 6.9 percent in cigarette smokers who did not inhale, 10.6 percent in smokers of pipes and cigars, and 15.5 percent in the ex-smokers. Among the various risk factors examined, the strongest association was found for elevations in the serum cholesterol and the other blood lipids examined. Weaker associations were found for increased relative weight, high blood pressure, and tobacco use.

Agnese, et al. *(2)* examined 265 patients in Italy aged 20 to 65 years who had myocardial ischemia. Patients were matched with an equal number of controls by age. A number of risk factors for CHD were measured in both groups. Cigarette smoking and elevated serum cholesterol were identified as major risk factors for CHD, particularly for individuals under the age of 50.

Boudik *(10)* found the prevalence of myocardial infarction to be significantly ($P < .001$) higher in cigarette smokers than in nonsmokers in a population of 8,292 Czechoslovakian men between the ages of 52 and 67.

Storch, et al. *(60)*, Estandia Cano, et al. *(17)*, and Jakuszewska *(30)*, in studies in Germany, Mexico, and Poland of CHD in individuals under the age of 40, reported that cigarette smoking was the dominant factor in the development of CHD in these patients.

Golovchiner *(21)* found cigarette smoking to be a significant factor in the development of myocardial infarction in a study of 530 patients with CHD in Leningrad hospitals.

Three studies without control groups from New Zealand *(59)*, Nepal *(47)*, and India *(58)* reviewed the prevalence of various risk factors, including cigarette smoking in populations with documented CHD.

12. CASCIU, G., MARRACCINI, L., ZEDDA, S., CARTA, G., FULGILE..., G. Sulla frequenza delle cardiovasculopatie tra gli operai dell'industria estrattiva della sardegna. Nota II: Incidenza in rapporto all'abitudine al fumo e all'alcool. (On the incidence of cardiovascular disease among the workers of the mining industry of Sardinia. Second communication: Incidence in relation to habitual smoking and consumption of alcohol.) Rassegna Medica Sarda 71(Supplement 1): 191-200, 1968.

35. KORNITZER, M., DEMEESTER, M., DELCOURT, R., BERNARD, R. Cardiopathies ischémiques dans une population d'employés de Bruxelles. Etude de la prévalence des cardiopathies ischémiques en fonction de la classe socio-économique. (Ischemic heart disease in a Brussels bank clerk population. Study of the prevalence of ischemic heart diseases as a function of socioeconomic class.) Revue d'Epidemiologie Medecine Sociale et Santé Publique 19(7): 599-612, October-November 1971.

36. KORNITZER, M., DEMEESTER, M., DELCOURT, R., GOOSSENS, A., BERNARD, R. Enquête cardio-vasculaire prospective dans une population sélectionnée: resultats de l'enquête initiale. (Prospective cardiovascular studies in a selected population. Results of the initial study.) Acta Cardiologica 26: 265-343, 1971.

37. KORNITZER, M., DEMEESTER, M., DENOLIN, H. Enquête dans une population d'employés. Relation des habitudes tabagiques avec d'autres parametres. (Investigation of a white-collar population. Relation of tobacco habits to other parameters.) Bruxelles Medical 51(10): 687-691, October 1971.

2. AGNESE, G., CANEPA, R., LA ROCCA, M. Eta e valore di alcuni indici per la discriminazione fra soggetti normali ed ischemici. (Age and value of several indices for discrimination in normal and ischemic subjects.) Giornale di Igiene e Medicina Preventiva 11(3): 140-151, July-September 1970.

10. BOUDIK, F. Srdecni infarkt a koureni. (Myocardial infarction and smoking.) Casopis Lekaru Ceskych 110(28): 814-820, July 25, 197...

60. STORCH, H., ENGELMANN, L., KOHLER, H. Der Herzinfarkt im jüngeren Legensalter. (Myocardial infarct in young people.) Deutsche Gesundheitswesen 26(34): 1593-1600. August 1971.

17. ESTANDIA CANO, A., ESQUIVEL AVILA, J., MALO CAMACHO, R., PEREZ SANTANDER, S., LEON MONTANEZ, E. Infarto juvenil del miocardio. (Myocardial infarction in the younger age groups.) Archivos de Instituto de Cardiologia de Mexico 41(2): 137-150, March-April ...

30. JAKUSZEWSKA, R. Zawal serca u osob mlodych. (Myocardial infarct in young subjects.) Wiadomosci Lekarskie 22(19): 1749-1752, October 1, 1969.

21. GOLOVCHINER, I. Y. Nekotoryye sotsial'nyye faktory zabolevaye... infarktom miokarda. (Some social factors in the incidence of myocardial infarct.) Zdravookhraneniе Rossiiskoi Federatsii 15(9): 12-14, 1971.

59. SMYTH, A. J., APPY, H., LANGLEY, R. B. An epidemiological surv... of ischemic heart disease. New Zealand Medical Journal 71(...: 284-286, May 1970.

47. PANDEY, M. R. Myocardial infarction in Nepal. Indian Heart J... 22(2): 73-82, April 1970.

58. SINGH, A. P., SINGH, S. P. Coronary heart disease—some epidemiolo... clinical and electrocardiographic observations. Journal of the Association of Physicians of India 19(9): 629-635, September 1971.

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Blood Lipids

In most of the following studies where the effect of cigarette smoking on blood lipids was examined, there was no control for dietary factors that may independently affect serum lipid levels. Schwartz, et al. *(56)* examined serum lipids in relation to smoking habits and relative weight in 7,972 male employees of the Parisian Civil Service in the city of Paris. Cigarette smoking was associated with a slight but significant ($P < .001$) increase in serum cholesterol. The authors found a positive correlation between increased relative weight and serum cholesterol levels, and a negative correlation between relative weight and smoking habits. These factors would operate in such a way as to reduce the apparent effect of cigarette smoking on the cholesterol levels. After controlling for relative weight, however, the investigators found a significant ($P < .001$) positive relationship between smoking and serum cholesterol.

56. SCHWARTZ, D., RICHARD, J. L., LELLOUCH, J., CLAUDE, J. R. Serum lipids, smoking and body build. Study of 7,972 actively employ males. Revue Europeenne d'Etudes Cliniques et Biologiques 16: 529-536, 1971.

In a study of various factors in relation to the mean serum cholesterol, Pincherle *(48)* examined the following parameters: blood pressure, height, weight, and skinfold thickness, X-ray findings of the chest and abdomen, the electrocardiogram, and smoking history. Ten thousand British business executives between the ages of 25 and 65 were examined. A significant association was found between elevated serum cholesterol, obesity, elevated systolic blood pressure, inadequate exercise, radiographic evidence of arterial calcification of the iliac arteries, and certain other factors. The increase observed in mean serum cholesterol with increasing number of cigarettes smoked was not statistically significant.

48. PINCHERLE, G. Factors affecting the mean serum cholesterol. Jou of Chronic Diseases 24(5): 289-297, August 1971.

Romslo *(53)* studied the distribution of serum lipids in 324 Norwegian military recruits. Cigarette smokers had a small but insignificant increase in serum triglycerides. No elevation was found for serum cholesterol. The subjects were young, and most smokers had only smoked for a few years.

53. ROMSLO, I. Distribution of serum lipids in Norwegian recruits. Acta Medica Scandinavica 190(5): 401-406, November 1971.

Burney and Enslein *(11)* investigated changes in clinical laboratory tests as related to aging and smoking in a 5-year study of 502 healthy male veterans. It was found that five variables were needed to predict age-related changes in those over 50. These were: fasting blood glucose, 2-hour post-glucose blood sugar, total serum protein, hemoglobin, and cholesterol esters. No significant differences in the laboratory data between smoking and nonsmoking subgroups were found.

11. BURNEY, S. W., ENSLEIN, K. Investigation of changes in clinical laboratory tests related to aging and smoking. Aging and Human Development 3(1): 95-101, February 1972.

Vlaicu, et al. *(70)* examined the interaction of cigarette smoking with blood pressure and serum lipids in 100 patients with angina pectoris who were between the ages of 40 and 59. Half the patients were smokers using more than 25 cigarettes a day. The smokers had lower serum lipids and lower blood pressure than the 50 nonsmoking patients with angina pectoris.

70. VLAICU, R., MACAVEI, E., PATIU, I. Studiu transversal ("cross-sectional") al presiunii arteriale si al lipidelor serice la coronarieni fumatori si nefumatori. (Cross-sectional study of arterial pressure and serum lipids in coronary smokers and nonsmokers.) Medicina Interna 23(8): 925-930, August 1971.

Mitwrzynska-Stryjecka, et al. *(43)* found that cigarette smoking immediately following a fatty meal did not significantly alter the serum free fatty acid, esterified fatty acid, cholesterol, or plasma turbidity levels over control values.

43. MITWRZYNSKA-STRYJECKA, W., WIDOMSKA-CZEKAJSKA, T., RUPNIEWSKA, Z. Wplyw palenia papierosow na lipemie po posilku tluszczowym. (The effect of acute experiment of cigarette smoking on lipaemia following fat meal.) Polski Tygodnik Lekarski 25(7): 251-253, February 16, 1970.

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Smoking and Blood Lipids. This citation is inserted among reports dealing on normal individuals. The observations of (70) Vlaicu et al. were made on 100 patients with angina pectoris. It is important because the study indicates that in patients, smoking does not modify serum lipid levels. The Summary is as follows:

SUMMARY

R. Vlaicu, Emilia Macavei, I. Papiu — CROSS-SECTIONAL STUDY OF ARTERIAL PRESSURE AND SERUM LIPIDS IN CORONARY SMOKERS AND NON-SMOKERS

Arterial pressure, cholesterol, total lipemia and serum beta-lipoproteins were studied in 100 patients with painful ischemic cardiopathy, aged 40 to 59 years, of whom 50 smoking over 25 cigarettes a day and 50 non-smokers.

The statistical difference between the two groups was significant, arterial pressure and blood lipids presenting higher values in the non-smokers, than in smokers.

It is considered that in coronary smokers, in the absence of other risk factors (high arterial pressure and serum lipid levels), smoking is the main risk factor. In the production of coronaropathy, smoking does not appear to act by modifying blood pressure and/or serum lipid levels.

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Ciampolini, et al. *(15)* examined the effects of cigarette smoking on blood lipid values in 10 healthy volunteers between the ages of 20 and 40. Cigarette smoking resulted in a prompt rise in free fatty acids and a delayed rise in serum triglycerides.

The relationship between cigarette smoking and changes in various serum lipid levels has not been clearly determined. Studies in this area continue to present conflicting results.

15. CIAMPOLINI, E., DRINGOLI, R., RAVAIOLI, P. Azione del fumo di sigarette su alcuni parametri del ricambio lipidico. (Action of cigarette smoking on several parameters of lipid metabolism.) Atti dell'Accademia dei Fisiocritici in Siena; Sezione Medico-Fisica 17: 474-480, 1968.

Electrocardiogram

Wysokinski *(76)* examined the effect of smoking on certain parameters of cardiovascular function in 100 healthy nonsmokers and 100 healthy smokers who were military recruits 19 to 25 years of age in Poland. Significant prolongation of the QRS interval ($P < .001$), flattening of the T wave, and ST segment depression following exercise were seen more frequently in the smokers than in the nonsmokers.

76. WYSOKINSKI, Z. Effects of tobacco smoking on certain parameters reflecting the condition of the circulatory system at rest and during exercise. Polish Medical Science and History Bulletin 14(2): 73-76, April 1971.

Van Buchem, et al. *(69)* examined the occurrence and significance of extrasystoles and conduction disorders in 760 healthy Dutch men between the ages of 40 and 67 who were followed for seven years. The presence of extrasystoles was not correlated with cigarette smoking or elevated serum cholesterol and was not associated with the development of CHD over the 7-year period.

69. VAN BUCHEM, F. S. P., DRION, E., WIGBOUT, H., BOSSCHIETER, E., FRIPA, J. R. Het voorkomen en de betekenis van extrasystolen en geleidingsstoornissen. Een 7-jarige longitudinale studie (I). (The occurrence and significance of extrasystoles and conduction disorders. A longitudinal study over 7 years (I).) Nederlands Tijdschrift voor Geneeskunde 114(7): 281-286, February 14, 1970.

Kattus, et al. *(33)* tested 314 healthy males 23 to 82 years of age for ischemic ST segment depression on the ECG during or after sub-maximal exercise. The abnormal ST segment depression identified in 30 subjects was correlated significantly with elevated serum cholesterol, abnormal resting ECG, and a history of cardiac symptoms but not with smoking, high blood pressure, physical inactivity, or family history of coronary disease.

33. KATTUS, A. A., JORGENSEN, C. R., WORDEN, R. E., ALVARO, A. B. ST-segment depression with near-maximal exercise in detection of preclinical coronary heart disease. Circulation 44(4): 585-595, October 1971.

Van Buchem, et al. *(68)* found no significant association between cigarette smoking and ischemic ST segment depression on ECG in 120 apparently healthy men who demonstrated this abnormality among a population of 760 men 50 to 70 years of age.

68. VAN BUCHEM, F. S. P., DRION, E., WIGBOUT, H., BOSSCHIETER, E. Het voorkomen en de betekenis van een depressie van het ST-segment in het elektrocardiogram bij mannen zonder andere verschijnselen. Een 7-jarige longitudinale studie (II). (The occurrence and the significance of a depression of the ST segment in the ECG of men free from other symptoms. A longitudinal study of 7 years (II).) Nederlands Tijdschrift voor Geneeskunde 114(8): 320-332, February 21, 1970.

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Smoking and the Electrocardiogram. One would conclude after reading this section that in some studies, smoking did not influence the ECG. Only the first study by (76) Wysokinski did something different from the others. He had subjects smoke 5 cigarettes and perform exercise. The abnormal electrocardiogram appeared as an acute effect on smoking and exercising. The Table of Results is quoted below.

The other 3 investigations were comparing the electrocardiogram of smokers and nonsmokers without smoking excessively prior to the recording. There is therefore no inconsistency in the conclusions that there is no significant association between smoking and the ischemic pattern of the electrocardiograph.

Smoking of 5 cigarettes had an evidently harmful effect on the circulatory system; the number of abnormal reactions was almost double in relation to the number of abnormal reactions in the studied subjects before smoking, the difference being statistically significant ($p < 0.01$). The harmful effect of tobacco smoking was even more evident in the group of smokers after smoking of cigarettes, as compared to the control group. These differences were highly significant statistically ($p < 0.01$).

The ECG investigation showed also a harmful effect of cigarette smoking on the circulatory system. After smoking of cigarettes at rest a statistically significant prolongation of the P wave was observed ($0.20 > p > 0.10$) and of the PQ segment ($0.30 > p > 0.20$). (Table II). The effort after smoking of cigarettes caused a statistically significant prolongation of the QRS complex ($p > 0.01$). After smoking of cigarettes before Letunov's test abnormalities of ECG appeared with flattening of T wave, depression of ST segment, more rarely with grade I atrioventricular block. These differences were statistically highly significant ($p < 0.01$), as compared with the number of abnormal ECG records in the smokers before smoking of cigarettes, as well as in the control group (10).

TABLE II

Effect of smoking on ECG

Parameter	Mean value of parameter in group			Comparison of mean values in groups					
	Non-smokers A	Smokers		A - B		A - C		B - C	
		before smoking B	After smoking C	Difference	Risk of error	Difference	Risk of error	Difference	Risk of error
P wave	0.0997	0.1015	0.1042	+0.0018	0.20>p>0.10	+0.0045	0.05>p>0.02	+0.0027	0.30>p>0.10
PQ segment	0.1435	0.1446	0.1537	+0.0059	0.10>p>0.05	+0.0102	p<0.01	+0.0043	0.30>p>0.20
QRS complex	0.0795	0.0809	0.0918	+0.0014	0.50>p>0.40	+0.0063	0.01>p>0.001	+0.0111	0.02>p>0.01
T wave	0.1316	0.1370	0.1496	+0.0054	0.25>p>0.02	+0.0180	0.20>p>0.10	+0.0126	0.02>p>0.01

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

Experimental Studies

Cigarette Smoke

Studies in Man

Summers, et al. *(61)* examined the effect of cigarette smoking on cardiac lactate metabolism in 15 patients with severe angina pectoris who had at least 75 percent obstruction in each of two or three major coronary vessels. All patients had been long-term cigarette smokers. Cigarette smoking produced increases in heart rate, systolic aortic pressure, the systolic ejection period per minute, and the tension-time index per minute, but lactate production was not induced by smoking in any patient who did not also have lactate production in the control state. In three patients with lactate abnormalities prior to smoking, inhalation of cigarette smoke sustained and slightly aggravated this condition.

61. SUMMERS, D. N., RICHMOND, S., WECHSLER, S. M. Cigarette smoke: Effects on lactate extraction in the presence of severe coronary atherosclerosis. American Heart Journal 82(4): 458-467, October 1971.

Studies in Animals

The effect of inhalation of cigarette smoke on ventricular fibrillation threshold (VFT) in normal dogs and dogs with experimentally produced acute myocardial infarction was studied by Bellet, et al. *(6)*. Mongrel dogs weighing 25 to 30 kilograms were anesthetized with sodium pentobarbital, and respiration was maintained using a Harvard ventilator attached to an endotracheal tube. In one group the electrical impulses used to precipitate ventricular fibrillation were delivered through the chest wall, and in another group the impulses were delivered directly to the heart through electrodes implanted in the myocardium. The experimental group of dogs were exposed to the smoke of three cigarettes over a 10-minute period. Each cigarette contained approximately 2 mg. of nicotine. With acute myocardial infarction, the VFT was significantly ($P < .001$) decreased, but in both the normal and myocardial infarction groups cigarette smoking resulted in a decrease in VFT that averaged 30 to 40 percent of the control value (figure 4). These findings are of interest in view of the increased incidence of sudden death observed among coronary patients who are heavy cigarette smokers *(65)*.

6. BELLET, S., DeGUZMAN, N. T., KOSTIS, J. B., KOUAN, L., FLEISCHMANN, The effect of inhalation of cigarette smoke on ventricular fibrillation threshold in normal dogs and dogs with acute myocardial infarction. American Heart Journal 83(1): 57-76, January 1972.

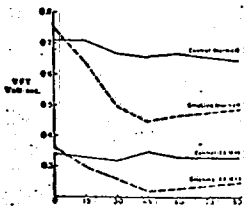

Figure 4.—The effect of cigarette smoke inhalation on the ventricular fibrillation threshold (VFT) of normal dogs and dogs with experimentally produced acute myocardial infarction (AMI).

SOURCE: Bellet, S., et al. *(6)*.

The effects of passively inhaled cigarette smoke on several measures of cardiovascular function in treadmill-exercised dogs were examined by Reece and Ball *(52)*. The experimental dogs were trained on the treadmill for approximately one year before exposure to cigarette smoke began. Each dog was passively exposed to the smoke of 36 cigarettes over a 3-hour period five days a week in a 2.2 m^3 chamber ventilated at the rate of seven exchanges per hour. The dogs were exposed to this cigarette smoke and were continued on their

52. REECE, W. O., BALL, R. A. Inhaled cigarette smoke and treadmill-exercised dogs. Archives of Environmental Health 24(4): 262-270, April 1972.

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Cigarette Smoke and Lactate Extraction. The report of (61) Summers et al. is an important one because it relates directly to the influence of cigarette smoking on patients with severe angina pectoris. It is more relevant than the observations of Aronow and Rakow discussed in page 483 (a). Lactate production of the myocardium was used by Summers as criteria for ischemia whereas exercise tolerance was used by Aronow and Rakow.

Portions of the Introduction, Discussion and Summary of (61) Summers et al. are quoted as follows:

Epidemiologic studies have demonstrated a significant relationship between cigarette smoking and obliterative vascular disease.[1] Of clinical importance is the significant relationship between cigarette smoking, myocardial infarction, and sudden death. Several studies[2-5] show an increase in deaths from coronary disease in cigarette smokers.

The objectives of this study were to determine whether the inhalation of cigarette smoke could acutely induce myocardial ischemia as reflected by abnormal myocardial lactate metabolism in patients with severe diffuse obstructive coronary artery disease, to compare this situation to the effects of catecholamine administration, and to measure some of the hemodynamic responses to the inhalation of cigarette smoke.

The absence of lactate production during smoking must be further considered. It might mean that the hemodynamic changes induced were not sufficient to cause myocardial ischemia, or that the method used was insufficiently sensitive to determine this occurrence. It would seem that the former was more likely since clinical expression of ischemia in the form of angina pectoris is not more frequently associated with smoking[7] and might be expected to be so if ischemia was produced. Another alternative would be that coronary blood flow was increased in these patients. Regan and associates[11] found no increase in coronary flow in subjects with coronary artery disease during smoking. Finally, nicotine might cause regional flow redistribution to the benefit of potentially underperfused areas. Evaluation of this possibility awaits the availability of methods for studying regional flow in the intact heart.

Summary

Fifteen patients with angiographically demonstrated severe obstructive coronary artery disease were the study subjects. Hemodynamic measurements were made before and during cigarette smoking, and metabolic evaluation was performed in these states and during isoproterenol stress. Heart rate, aortic pressure, systolic ejection and diastolic filling periods were measured. Myocardial lactate extraction was evaluated at three coronary sinus drainage sites. Despite increases in heart rate, aortic pressure, the systolic ejection period per minute, and the tension-time index per minute lactate production was not induced by smoking in any patient without lactate production in the control state. In 3 patients with lactate abnormalities prior to smoking, inhalation of cigarette smoke sustained and slightly aggravated this circumstance. Isoproterenol induced lactate production in all but 1 patient.

Cigarette smoking in a group of patients with severe obstructive coronary artery disease did not produce evidence of ischemia as determined by abnormalities in lactate extraction.

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exercise program for an additional year. Exposure to cigarette smoke was associated with cardiac enlargement, ST segment depression, and an increase in post-exercise serum lactate concentrations.

Nicotine

Studies in Man

Isaac and Rand (28) have recently described a method for the assay of plasma nicotine. An alkali flame ionization detector was used with a gas-liquid chromatograph. The test is sensitive to 1 ng./ml. of nicotine in a 2.5 ml. sample. Thirty minutes elapsed between end of one cigarette and start of next. Blood samples were taken before smoking and at 0.5, 10, and 30 minutes after the last puff of each cigarette. Plasma nicotine levels increased rapidly during cigarette smoking (figure 5). The post-smoking decay curve consisted of two components: an initial rapid phase which may be due to the uptake of nicotine from the blood by various tissues, and a slower phase which may represent metabolism and excretion of nicotine. Some accumulation of plasma nicotine occurred during a day of smoking, but the background level never approached the peaks attained during and immediately following active cigarette smoking. The rate of elimination was rapid enough to prevent any appreciable accumulation of nicotine from one day to the next. The development of sensitive tests of plasma nicotine levels will allow a greater understanding of various dynamics of smoking. Inhalation patterns can be objectively measured, and the role of nicotine in habituation to cigarettes can be evaluated.

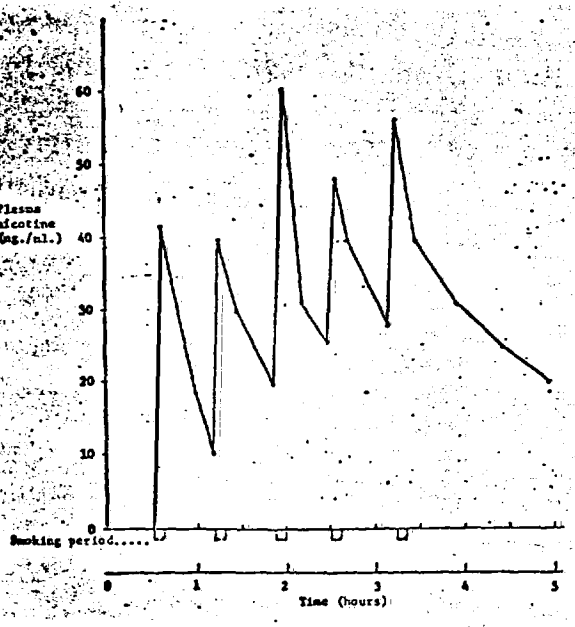

Figure 5.--Effects of smoking five consecutive cigarettes on plasma nicotine concentration.

SOURCE: Isaac, P. F., Rand, M. J. (28).

28. ISAAC, P. F., RAND, M. J. Cigarette smoking and plasma levels of nicotine. Nature 236(5345): 302-310, April 7, 1972.

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Studies in Animals

The effect of nicotine on regional blood flow in the canine heart was examined by Mathes and Rival *(41)*. The effects of nicotine were examined in normal hearts and after partial coronary artery occlusion. Under normal circumstances, as well as after infusion of nicotine in normal hearts, the subendocardial portion of the myocardium had a 9.5 percent greater capillary flow than the subepicardial fraction. Partial ligation of the coronary arteries resulted in a 22.8 percent reduction in left ventricular blood flow; however, the subendocardial portion remained 8.6 percent higher than in the epicardium. After coronary artery ligation, an infusion of nicotine resulted in a significant ($P < .001$) reduction in the capillary flow of the inner portion of the myocardium relative to the outer part.

41. MATHES, P., RIVAL, J. The effect of nicotine on regional blood flow in the canine heart. Proceedings of the Society for Experimental Biology and Medicine 138(1): 361-364, October 1971.

Bhagat, et al. *(7)* examined the effect of cigarette smoking on the cardiovascular system of dogs. Various pharmacological agents, e.g., tyramine hydrochloride, propranolol, and chlorisondamine, were used to modify the evoked response to tobacco smoke in order to clarify the mechanisms producing the observed effects. The authors concluded that the more important actions of nicotine include a stimulation of sympathetic ganglia and the adrenal medulla and the release of catecholamines from sympathetic nerve endings and chromaffin tissue.

7. BHAGAT, B., RUEHL, A., RIO, P., RAMA, M. W., HUGHES, M. J. Effect of cigarette smoke on the cardiovascular system in dogs. Proceedings of the Society for Experimental Biology and Medicine 137(3): 969-972, July 1971.

Bing, Hellberg, and associates *(8, 25)* studied the microcirculation of the left atrium of anesthetized cats by direct visualization using high speed cinematography. Nicotine injections produced a slight but insignificant increase in red cell velocity in the capillary circulation during both systole and diastole.

8. BING, R. J., WAYLAND, H., RICKART, A., HELLBERG, K. Studies on the coronary microcirculation by direct visualization. Giornale Italiano di Cardiologia 1: 401-408, September-October 1971.

25. ——, K., WAYLAND, H., RICKART, A. L., BING, R. J. Studies on the coronary microcirculation by direct visualization. American Journal of Cardiology 29: 593-597, May 1972.

The effects of nicotine on the biosynthesis of various lipid fractions in the aorta of dogs were studied by Kupke *(40)*. After nicotine administration, significant reduction occurred in the formation of free (^{14}C)-sterols, while elevated levels of unesterified fatty acids were formed in the media and intima of these *in vitro* specimens. The author suggested that nicotine may impair oxidative enzyme systems possibly by damaging the mitochondrial structures, thereby leading to lipid accumulation in the aorta.

40. KUPKE, I. R. Biosynthesis of lipids in perfused dog aorta and coronary artery. II. Incorporation of (2-^{14}C) acetate into lipids of two aortic layers and of the coronary artery under the influence of nicotine. Journal of Molecular and Cellular Cardiology 4(1): 27-38, February 1972.

Schievelbein and Eberhardt *(54)* reviewed the cardiovascular actions of nicotine and smoking.

54. SCHIEVELBEIN, H., EBERHARDT, R. Cardiovascular actions of nicotine and smoking. Journal of the National Cancer Institute 48(6): 1785-1794, June 1972.

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Nicotine on Regional Coronary Blood Flow. The observations of (41) Mathes and Rival need further comments to place them in proper perspective. The reduction in blood flow in the subendocardial portion is not unique for nicotine but for drugs including catecholamines that influence intraventricular pressure.

Nicotine was administered by infusion large enough to cause a rise in blood pressure of from 119/86 to 154/108. This degree of pressor effect is not encountered in ordinary smoking. Portions of the Introduction and Comments are quoted below:

> Nicotine administration elicits a number of complex cardiovascular responses the precise mechanisms of which are not clearly understood. The hemodynamic effects, which have been attributed chiefly to the release of catecholamines, consist mainly of an increase in arterial pressure, heart rate, and stroke work and a resultant increase in coronary blood flow (1–3). The susceptibility of regional myocardial blood flow to changes in ventricular pressure and coronary perfusion has been demonstrated in this laboratory (4), as well as by other investigators (5–7). The present investigations were aimed at studying the effect of nicotine on the regional distribution of capillary flow in the canine heart. The perfusion of the subendocardial portion of the left ventricle was examined because this area has been shown to be especially vulnerable to changes in coronary perfusion and arterial pressure (4, 6, 7). Coronary blood flow was measured by an electromagnetic flowmeter, and the regional distribution of blood flow was estimated by uptake of ^{86}Rb after a bolus injection as reported previously (4).

> When partial occlusion of coronary arteries was followed by nicotine administration (Group IV), the blood pressure increased again. Under these circumstances ^{86}Rb uptake in subendocardial tissue was less than in subepicardial layers, and was markedly reduced in comparison to the normally perfused septum. This is indicative of a reduction in capillary flow to the inner portion of the myocardium as compared to septal and subepicardial flow. These changes are significant in comparison to the control and are accompanied by marked ECG changes. It appeared thus that the administration of nicotine in the presence of partial coronary artery stenosis resulted in a decrease in relative subendocardial perfusion, despite an increase in the total coronary flow. These effects may be related to the release of catecholamines (1), and similar observations have been made after the administration of norepinephrine under these circumstances (4).

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Carbon Monoxide

Studies in Man

Numerous articles have recently been published on the various effects of carbon monoxide on man and animals and are of particular interest because of the relatively high levels of carbon monoxide found in the main and sidestream smoke of cigarettes. Only those articles are discussed here which contain data on the cardiovascular effects of carbon monoxide.

Aronov and Rokav *(3)* examined the effects of smoking-induced carboxyhemoglobin levels on angina pectoris in 10 patients with CHD. The time to the onset of angina after smoking a non-nicotine cigarette was measured. Each patient had smoked more than a pack of cigarettes a day for at least 19 years and had a classical history of exertional dyspnea. Smoking non-nicotine cigarettes failed to result in an elevation of the blood pressure or the heart rate; however, there was a significant ($P < .01$) increase in COHb levels to about 8 percent. This resulted in a significant decrease in exercise performance compared to the nonsmoking state ($P < .01$). This confirms that carbon monoxide can compromise oxygen delivery independently of the effect of nicotine.

3. ARONOV, W. S., ROKAV, S. W. Carboxyhemoglobin caused by smoking non-nicotine cigarettes. Effects in angina pectoris. Circulation 44(5): 782-788, November 1971.

Maximal oxygen consumption under conditions of carbon monoxide intoxication were studied in human volunteers by several authors *(49, 71, 72)*. COHb levels of 15 or 20 percent resulted in a proportionate reduction in maximal O_2 consumption. The volunteers responded to the decrease in oxygen-carrying capacity of the blood with a tachycardia and relative hyperventilation during moderate exercise. Carbon monoxide produces a limitation of an individual's maximal oxygen consumption by decreasing the availability of oxygen supplied under conditions of increased oxygen demand.

49. PIRNAY, F., DUJARDIN, J., DENOANNE, R., PETIT, J. M. Muscular exercise during intoxication by carbon monoxide. Journal of Applied Physiology 31(4): 573-575, October 1971.

71. VOGEL, J. A., CLESER, N. A. Effect of carbon monoxide on oxygen transport during exercise. Journal of Applied Physiology 32(2): 234-239, February 1972.

72. VOGEL, J. A., CLESER, N. A., WHEELER, R. C., WHITTEN, B. K. Carbon monoxide and physical work capacity. Archives of Environmental Health 24(3): 199-203, March 1972.

Heistad and Wheeler *(24)* reported that the hypoxia induced by carbon monoxide inhalation caused an inhibition of reflex vasoconstrictor responses despite the presence of normal arterial oxygen tension.

24. HEISTAD, D. D., WHEELER, R. C. Effect of carbon monoxide on reflex vasoconstriction in man. Journal of Applied Physiology 32(1): 7-11, January 1972.

Studies in Animals

The effects of carbon monoxide on coronary hemodynamics and left ventricular function in six unanesthetized dogs were studied by Adams, et al. *(1)*. The animals reacted to a 5 percent carboxyhemoglobin level with a 14 percent increase in coronary blood flow. Twenty percent COHb resulted in a 57 percent increase in coronary flow and slight increases in heart rate and stroke volume.

1. ADAMS, J. D., ERICKSON, H. H., STONE, H. L. The effects of carbon monoxide on coronary hemodynamics and left ventricular function in the conscious dog. IN: Proceedings of the 1st Annual Conference on Environmental Toxicology, September 9-11, 1970. Aerospace Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio, AMRL-TR-70-102, December 1970. pp. 107-110.

Birnstingl, et al. *(9)* exposed young adult rabbits to 400 p.p.m. CO for periods that varied from 6 to 14 hours. The mean COHb level after a series of 22 exposures was 17 percent. A qualitative increase in platelet stickiness, as measured by the bead-column method, developed during the 24-hour period following CO exposure. The authors observed that this "...provides a possible mechanism for intimal deposition and a further link in the association between habitual smoking and peripheral vascular disease." Astrup *(5)* found the cholesterol level in the aorta of rabbits exposed to a low level of carbon monoxide for 10 weeks to be, on the average, 2.5 times higher than in the control rabbits. Both the experimental and control groups were maintained on a high cholesterol diet.

9. BIRNSTINGL, M. A., BRIMSON, K., CHAKRABARTI, B. K. The effect of short-term exposure to carbon monoxide on platelet stickiness. British Journal of Surgery 58(11): 837-839, November 1971.

5. ASTRUP, P. Rökning och koronarsjukdom (II): Kateheskadigends virkning af CO og hypoxi. (Smoking and coronary disease (II): Vascular damaging effect of CO and hypoxia.) Läkartidningen 67(3): 44-49, January 14, 1970.

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Smoking-Induced Carboxyhemoglobin Level. The observations of (3) Aronow and Rokaw were made on patients. However, this does not mean that healthy smokers suffer from compromising oxygen delivery. The level of carboxyhemoglobin reported was about 8% which is higher than the 5% for smokers without heart disease.

The authors have recognized the possibility that other pollutants in the cigarette smoke have not been excluded. The reduced hemodynamic response to smoking has been interpreted by the authors as due to lessened oxygen available for the myocardium. Another way of interpretation is to regard the earlier onset of angina to be a protective mechanism that is not necessarily harmful to the patient.

This technique used for detecting myocardial ischemia should be compared with that described in page 480 (a) which arrived at a different conclusion.

There are theoretical grounds for concern that other inhaled gaseous pollutants, such as oxides of nitrogen, may also act to impair the hemoglobin-oxygen transport and delivery system. Further investigation of these mechanisms is clearly indicated.

Sarnoff and coworkers[11] have found the primary hemodynamic determinant of myocardial oxygen consumption to be the total tension developed by the myocardium (heart rate times the area under the systolic portion of the aortic pressure curve). The present study shows that the product of systolic blood pressure times heart rate after exercise-induced angina was significantly less after smoking the nonnicotine cigarettes than in the nonsmoking state. This suggests strongly that less myocardial work can be performed before the onset of angina in the presence of elevated carboxyhemoglobin levels, related to lessened oxygen available for the myocardium.

Smoking high-nicotine[1-3] or low-nicotine[2,3] cigarettes causes an increase in systolic blood pressure and in heart rate, thereby increasing the myocardial oxygen demand, but this is not found after smoking of nonnicotine cigarettes.[2,3] However, smoking high-nicotine, low-nicotine, or nonnicotine cigarettes does cause elevated carboxyhemoglobin levels,[4,5] decreasing the amount of oxygen available to the myocardium. Therefore, patients with historic angina pectoris develop pain sooner after exercise following smoking either high-nicotine cigarettes,[1] low-nicotine cigarettes,[2] or nonnicotine cigarettes, in relation to at least two factors: increased myocardial oxygen demand in the presence of nicotine, and impaired oxygen delivery, whether or not nicotine is present.

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Gibbons and Mitropoulos *(20)* reported that CO inhibited cholesterol biosynthesis with accumulation of lanosterol and 24,25-dihydrolanosterol in an *in vitro* system of rat liver homogenates exposed to a 90 percent CO atmosphere. It was felt that CO may have influenced an early step in the oxidative elimination of the 14α-methyl group of lanosterol.

Smoking and Thrombosis

Previous reports of the Surgeon General on smoking and health *(62, 63, 64, 65, 66)* have reviewed the effects of smoking on thrombosis. Recent reviews and studies have not thus far yielded a unifying concept of the effect of smoking on thrombosis *(4, 18, 19, 32, 45)*.

20. GIBBONS, G. F., MITROPOULOS, K. A. Inhibition of cholesterol biosynthesis by carbon monoxide: Accumulation of lanosterol and 24,25-dihydrolanosterol. Biochemical Journal 127(1): 315–317, March 1972.

4. ARTHES, F. G. An epidemiologic survey of hospitalized cases of venous thrombosis and pulmonary embolism in young women. Milbank Memorial Fund Quarterly 50(1, Part 2): 233–243, January 1972.

18. FACCHINI, G., SEMENARO, S., DI BIASE, G., TABARRONI, F., SPAGNOLO, AUTORE, A., BONAVITA, E. Modificazioni nel soggetto anziano della reattivita al fumo di sigaretta: Ricerche sull'equilibrio emocoagulativo e fibrinolitico e sul circolo periferico. (Modifications of the reactivity to cigarette smoke in old subjects: Research on the hemocoagulative and fibrinolytic equilibrium and on the peripheral circulation.) Giornale di Gerontologia 19(10): 779–784, 1972.

19. FEINLEIB, M. Venous thrombosis in relation to cigarette smoking, physical activity, and seasonal factors. Milbank Memorial Fund Quarterly 50(1, Part 2): 123–141, January 1972.

32. KÄPPERT, A. Tobacco and diabetic angiopathy. Acta Diabetologica Latina 8(Supplement 1): 429–433, September 1971.

45. ORLOVA, N. P. Some parallels between the blood coagulation activity and the condition of adrenergic and cholinergic system of the organism. Terapevticheskii Arkhiv 43: 58–62, February 1971.

CEREBROVASCULAR DISEASE

Paffenbarger and Wing *(46)* examined several precursors of nonfatal stroke in 102 patients with this disease in a population of 10,327 men who had attended Harvard University between the years of 1916 and 1940 and who also returned a self-administered questionnaire in 1966. Examination of University medical records of these former students revealed four characteristics present in youth that predisposed those individuals who were more likely to experience a nonfatal stroke in later life. These factors were: cigarette smoking, elevated blood pressure, increased weight for height, and short body stature. The age and interval-adjusted incidence rates per 1,000 were 10.1 for nonsmokers, 15.3 for smoker of 1 to 9 cigarettes, and 17.9 for smokers of 10 or more cigarettes a day. The relative morbidity ratios for the four factors cited above increased from 1.1 for patients with only one risk factor to 1.7 for those with any two risk factors, and to 3.2 for patients with any three or four risk factors.

Miyazaki *(45)* studied blood flow in the internal carotid artery using ultra sound techniques. Internal carotid blood flow was examined under a variety of experimental conditions. Inhalation of cigarette smoke in three individuals aged 27, 67, and 69 resulted in an increased blood flow due to decreased vascular resistance. This effect lasted for 10 to 20 minutes following smoking.

46. PAFFENBARGER, R. S., Jr., WING, A. L. Chronic disease in former college students. XI. Early precursors of nonfatal stroke. American Journal of Epidemiology 94(6): 524–530, December 197

45. MIYAZAKI, H. Studies on cerebral circulation by the ultrasonic Doppler technique--with special reference to clinical applica of the technique. In: Meyer, J. S., Schade, J. P. (Editors). Progress in Brain Research, Volume 35. Cerebral Blood Flow, Amsterdam, Netherlands, Elsevier Publishing Co., 1972. pp. 1-

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Unifying Concept of Effect of Smoking on Thrombosis. The studies cited are for special groups of patients who suffer from hypercoagulability unrelated to smoking. For example, (32) Kappert made his observations on diabetics with obliterative arteriosclerosis. The results of comparison are quoted below. The Conclusion does not apply to nondiabetic patients with coronary heart disease.

> A second group consisted of ten patients with obliterative arteriosclerosis, five of whom had diabetes mellitus (average age 54 years). These cases showed diffuse stenotic obliterative changes of the arterial system of the legs with occlusion in the femoro-popliteal region on one or both sides. Before the start of the treatment they all were heavy smokers (20-40 cigarettes daily). During the test period they had given up smoking for at least two weeks. Eight out of these ten patients showed a pathological thromboplastin tolerance test which was very marked in 4 (3 of whom were diabetics). The behaviour was strictly different from the control group. An exact quantitative assessment of the increased sensitivity to smoking is not possible. But correlating to the recalcification time values of the two curves, the augmentation of the clotting tendency during smoking was 18% for the whole group. In the cases of diabetes mellitus the average increase was 27%.

SUMMARY

With the aid of the so-called thromboplastin tolerance test an increased tendency towards intravascular clotting can be demonstrated. After the discussion of the principle of this test its application in normal individuals and in patients with arterial occlusive disease is analysed. Diabetics with obliterative arteriosclerosis show an increased sensitivity to smoking which provokes a state of higher clotting tendency. This is probably one of the mechanisms through which smoking favors the development of arteriosclerosis and the acceleration of its course. In our series the diabetics with arterial occlusive disease showed the most marked reaction to the thromboplastin tolerance test after smoking.

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PERIPHERAL VASCULAR DISEASE

The association between cigarette smoking and arteriosclerosis obliterans (ASO) was investigated by Weiss *(73)*. Patients were considered to have ASO if both the dorsalis pedis and posterior tibial pulses were absent in one lower extremity and the examining physician made a diagnosis of ASO. Patients were asked the age of initiation of smoking; the daily number of cigarettes smoked; the amounts smoked at ages 30, 50, and 70; the age at which they stopped smoking; and, for males, whether they smoked cigars or a pipe. A total of 214 male cases, 206 male controls, 350 female cases, and 913 female controls were studied. The control group was composed of patients with peripheral vascular problems other than ASO but who had dorsalis pedis pulses present on initial examination. In each age and sex group, cigarette smoking was more prevalent among cases than controls. In both sexes, risks were high for smokers of less than one pack a day, and increased with the amount smoked (figures 6 and 7). It was estimated that 70 percent of nondiabetic ASO in the United States is related to the use of cigarettes. Diabetes mellitus is a major risk factor for the development of ASO; however, cigarette smoking appeared to act independently of diabetes.

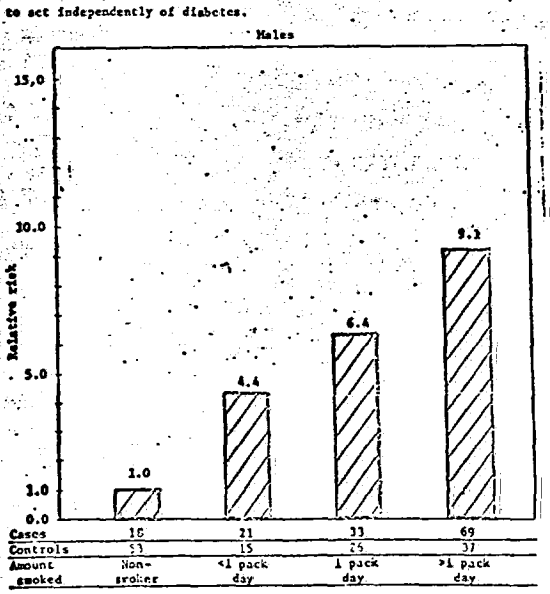

Figure 6.--Relative risk of developing arteriosclerosis obliterans (ASO) for males by amount of cigarettes smoked.

SOURCE: Weiss, N. S. *(73)*.

WEISS, N. S. Cigarette smoking and arteriosclerosis obliterans: An epidemiologic approach. American Journal of Epidemiology, 95(1): 17-25, January 1972.

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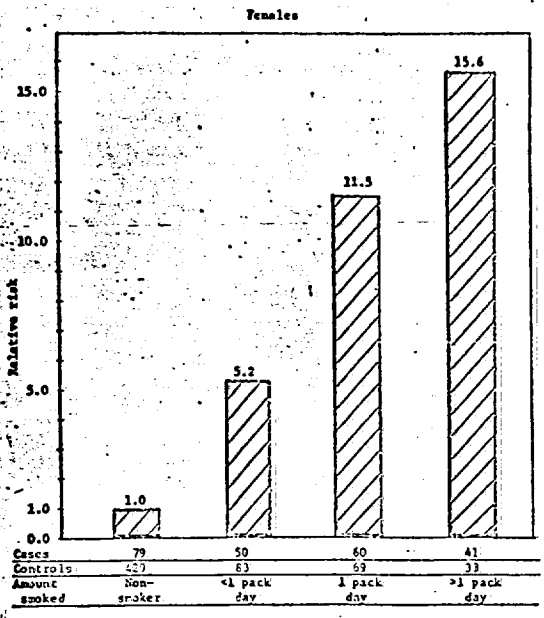

Figure 7.--Relative risk of developing arteriosclerosis obliterans (ASO) for females by amount of cigarettes smoked.

SOURCE: Weiss, N. S. *(73)*.

Preuss, et al. *(50)* examined the relationship between several factors including cigarette smoking, blood pressure, weight, and history of diabetes and the development of occlusive disease of the peripheral arteries in a population of 300 patients in Germany. Group I consisted of 150 patients with a mean age of 59 years who had intermittent claudication. Most of these patients were ambulatory. The 150 patients in Group II had a mean age of 60 years and had far advanced peripheral arteriosclerosis with ischemic pain at rest or evidence of gangrene. There was no control group of patients free of vascular disease. There were few nonsmokers in either group of patients, but the group with the more severe disease had a higher average daily consumption of cigarettes than did Group I.

PREUSS, E.-G., EDER, R., WELLER, F. Risikofaktoren bei peripheren arteriellen Verschlusskrankheiten unterschiedlichen Schweregrad. (Risk factors in occlusive diseases of the peripheral arteries, of varying severity.) Zeitschrift für die gesante innere Medizin und Ihre Grenzgebiete 25(10): 464-468, May 15, 1970.

The influence of cigarette smoking on late occlusion of aorto-femoral bypass grafts was examined by Wray, et al. *(75)*. A series of 100 patients who had aortic reconstruction for aneurysmal or aortoiliac occlusive disease between 1965 and 1968 were studied. Of the patients who had bypass grafts for occlusive disease, 30 patients smoked cigarettes and 16 did not. Late occlusions from thrombosis occurred in 9 patients, each of whom was smoking more than a pack of cigarettes a day at the time the thrombosis occurred ($P < .5$). The authors recommend cessation of cigarette smoking to all patients undergoing vascular reconstruction.

75. WRAY, R., DePALMA, R. G., MURAY, C. H. Late occlusion of aorto-femoral bypass grafts: Influence of cigarette smoking. Surgery 70(6): 969-973, December 1971.

Schnauss and Arlt *(55)*, Wilbert *(74)*, and Kradjian, et al. *(39)* reported a greater than 93 percent prevalence of cigarette smoking in three separate series of patients with severe peripheral vascular disease.

55. SCHNAUSS, A. K., ARLT, E. Morphologische Befunde, postoperative Komplikationen, Letalität und Liegedauer nach Amputation wegen Durchblutungsstörungen. (Morphological findings, postoperative complications, mortality and duration of bed rest following amputations occasioned by disorders of the peripheral circulation. Zeitschrift fur Ärztliche Fortbildung 64(2): 84-87, January 15, 1

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Isacsson *(23)* performed venous occlusion plethysmography in 684 men aged 55 in Malmö, Sweden. In addition to a detailed smoking history, a number of other factors were studied, including blood pressure, pulse, height, weight, ECG, heart volume, and blood lipids. The plethysmograms were taken on both legs simultaneously with the patient in the recumbent position. Measurements were taken at rest and during reactive hyperemia produced by obstructing arterial inflow to the legs for three minutes with a blood pressure cuff applied to the thigh. Smokers had a significantly lower mean flow capacity (MFC) than did nonsmokers. The MFC in the legs was reduced in direct proportion to the amount of tobacco consumed per day regardless of the mode of smoking. The MFC was significantly lower with inhalation ($P < .001$) and with increasing amount smoked ($P < .001$).

Matsubara and Sano *(42)* studied the effect of cigarette smoking on human precapillary sphincters of the leg using a pressure plethysmograph applied to the calf. Precapillary sphincter tone was estimated using the capillary filtration coefficient, which is the product of "functional capillary service area" and the filtration constant of the capillary wall. Four healthy male subjects were tested. All were regular smokers of cigarettes who had not smoked for the previous 24 hours. When cigarette smoke was inhaled deeply at 30-second intervals over a 12- to 15-minute period, there was a 19 percent decrease in the capillary filtration coefficient, indicating closure of precapillary sphincters. Cigarette smoking also resulted in a 31 percent decrease in calf blood flow, indicating some degree of constriction of the arterioles in the leg. The pressure volume curves of the venous system were not affected by cigarette smoking.

Halstad and Wheeler *(26)* examined the effect of carbon monoxide on vascular resistance and reflex vasoconstriction in the forearms of 12 healthy men 19 to 23 years old. After control measurements were taken, the subjects were exposed to enough carbon monoxide to produce carboxyhemoglobin levels of 18 to 20 percent or 25 percent. Carbon monoxide did not cause a change in alveolar PO_2 or PCO_2. The arterial oxygen saturation was less than 75 percent, but this decrease did not result in altered resting arterial pressure nor was there much evidence of sympathetic stimulation. Carbon monoxide hypoxia did result in a significant decrease in vascular resistance in the resting forearm ($P < .05$). Carbon monoxide exposure also resulted in a significant depression of the vasoconstrictor responses of the forearm following the application of negative pressure to the lower body ($P < .001$) and of ice on the forehead. It appears that the hypoxia induced by carbon monoxide causes an inhibition of reflex of vasoconstrictor responses despite the presence of normal arterial oxygen tension.

42. MILBERT, L. Nikotinkonsum und arterielle Verschlusskrankheit. (Nicotine consumption and arterial occlusive disease.) Medizinische Klinik 66(35): 1190-1192, September 3, 1971.

39. KRADJIAN, R., BOWLES, L. T., EDWARDS, W. S. Peripheral arterial disease in Ceylon. Surgery 69(4): 523-525, April 1971.

29. ISACSSON, S.-O. Venous occlusion plethysmography in 55-year old men. A population study in Malmö, Sweden. Acta Medica Scandinavica (Supplement 537): 1972. 62 pp.

42. MATSUBARA, I., SANO, T. Effect of cigarette smoking on human precapillary sphincters. British Journal of Pharmacology 45(1): 13-20, May 1972.

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SUMMARY OF RECENT CARDIOVASCULAR FINDINGS

In addition to the summary presented in the introduction to this chapter based on previous reports of the health consequences of smoking, the following statements are made to emphasize the recent developments in the field:

1. Recently conducted epidemiological studies from several countries continue to confirm that cigarette smoking is one of the major risk factors contributing to the development of coronary heart disease.
2. Epidemiological evidence suggests that black men in the rural South respond to the same risk factors for coronary heart disease, including cigarette smoking, as white men do but apparently at lower disease rates, which appears to be in part due to differences in physical activity.
3. Data from several epidemiological and experimental studies suggest that cigarette smoking is a major risk factor in the development of peripheral vascular disease. This may in part be due to the decreased blood flow in arterioles and capillaries associated with cigarette smoking. Smoking may complicate the surgical intervention in this disease by contributing to late occlusion of the treated vessel.
4. A laboratory test has been developed which accurately measures nicotine levels in blood. This test will be useful in understanding nicotine metabolism and can be used as an objective measure of cigarette smoke inhalation.

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Summary of Experimental Studies. The recent experimental work does not support the contention that smoking decreases blood flow in arterioles and capillaries. At least two types of evidence were mentioned: page 479 on electrocardiogram and page 480 on lactate extraction performed on healthy smokers and on patients with coronary heart disease who were also smoking cigarettes. The positive results appearing on page 483 were on smoking of nonnicotine cigarettes and on page 482 related to nicotine in animal heart. The conclusion in the document should state that recent evidence does not show that cigarette smoking decreases flow.

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XV. RECOMMENDATIONS TO THE COUNCIL FOR TOBACCO RESEARCH

There are two areas of investigation which it is important to elucidate further: the relationships between cigarette smoking and coronary heart disease. They are as follows:

A. Prospective studies of patients with angina pectoris or myocardial infarction. The primary aim of the investigation will be to identify patients with tobacco angina. This group will be compared with patients having effort angina with no previous history of infarction, postinfarction patients, and matched controls. The following will be examined: (1) smoking habits, (2) acute effects of cigarette smoking on carboxyhemoglobin, blood lipids and coagulability of the blood; (3) oxygen consumption and electrocardiogram at various levels of exercise; (4) determination of risk factors and the outcome of reducing one at a time; and (5) prognosis and development of complications. The list has been selected on the basis of the present state of knowledge derived from the considerable amount of information obtained from epidemiologic investigations.

B. Chronic effects of cigarette smoke in animals. A model that will allow measurement of cardiac function and detection of myocardial ischemia is necessary. In addition to the antemortem and postmortem examination of the heart, the following will be measured: carboxyhemoglobin level, extent of absorption of nicotine, coagulability of the blood, concentration of lipids in the blood, catecholamine excretio glucose tolerance and insulin assay. With the use of suitable animals exposed to cigarette smoke and of controls, one can obtain an answer to the question as to whether or not cigarette smoking causes coronary heart disease.

1005050842

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AUTHOR INDEX

(Reprint number) followed by pages in the text

ABEL 1971 (617) 203, 202
ABELSON 1968 (S 201) 337
ABOU-DAOUD 1968 (50) 35, 34, 33
ABRAMSON 1969 (A 177) 52
ACHESON 1960 (S 130) 332
ACHESON 1961 (541) 179, 166
ACHESON 1962 (272) 99, 98
ACHESON 1962 (A 241) 116
ACHESON and JESSOP 1961 (647) 211, 209, 354 (a)
ADACHI, ADACHI and POLLAK 1965 (945) 279, 278
ADAMS 1969 (S 206) 337
ADAMS 1970 (A 329) 139
ADAMS 1971 (S 213) 337
ADAMS 1969 (S 205) 337
ADLER and HAMMETT 1969 (A 294) 119
ADLER and HENSEL 1906 (946) 279, 277
AGNESE and BUONVINO 1964 (618) 203, 201
AGNESE, CANEPA and LA ROCCA 1970 (580) 182, 168
AHTEE and MATTILA 1966 (931) 276, 275
ALBERTINI, MARTINESI and GANDINI 1967 (932) 276, 275
ALBUTT 1915 (1) 19, 16
ALFANO, JOVINO and MUSELLA 1962 (99) 65, 62
ALFIN-SLATER 1969 (A 415) 145
ALIMURUNG 1964 (S 70) 328
ALLISON and ROTH 1969 (780) 242, 241
ALSCHULE 1970 (A 140) 49
ALTERKOSE 1968 (A 392) 143
ALTSCHULE 1963 (S 306) 345
ALVAREZ 1963 (S 190) 336
AMBRUS and MINK 1964 (844) 251, 250
AMERICAN HEALTH FOUNDATION 1972 (A 416) 145
AMERICAN HEART ASSOCIATION 1968 (A 417) 145
AMERICAN JOURNAL OF CLINICAL NUTRITION 1973 (S 265) 341
AMERICAN JOURNAL OF PUBLIC HEALTH 1964 (S 223) 339
AMERICAN JOURNAL OF PUBLIC HEALTH 1969 (S 243) 340
ANDERSON 1967 (453) 171, 160
ANDERSON 1970 (A 463) 188
ANDERSON 1971 (1047) 305, 303
ANDERSSON 1972 (1046) 305, 301
ANDRUS, MILLER, STALLONES, EHRLICH and JONES 1968 (464) 172, 162
ANFOSSI, ROSSI and SATTA 1967 (A 95) 31
ANJUERE 1968 (529) 178, 165
ANONYMOUS 1964 (S 140) 333
ANONYMOUS 1963 (S 297) 345
ANONYMOUS 1965 (S 298) 345
ANONYMOUS 1968 (528) 178, 165
ANONYMOUS 1970 (S 303) 345
ANONYMOUS 1963 (S 295) 345
ANONYMOUS 1967 (S 299) 345
ANONYMOUS 1969 (S 301) 345
ANONYMOUS 1969 (S 300) 345
ANONYMOUS 1969 (S 207) 337
ANONYMOUS 1970 (S 302) 345
ANONYMOUS 1972 (S 304) 345
ANONYMOUS 1968 (S 48) 326
ANONYMOUS 1963 (S 296) 345
ANONYMOUS 1971 (S 305) 345
ANSCHUTZ and BERG 1968 (A 33) 27
ANSELMINO and BOSCO 1967 (S 46) 326
ANTON 1967 (A 747) 262
ARAI, PORDY, CHESKY and MASTER 1951 (2) 19, 18
ARAVANIS and CORCONDILAS 1972 (100) 66, 63
ARAVANIS, DONTAS, LEKOS and KEYS 1967 (553) 180, 166
ARDLIE, GLEW and SCHWARTZ 1966 (971) 284, 282
ARMITAGE 1965 (A 691) 257
ARMITAGE, MILTON and MORRISON 1965 (A 748) 262
ARMSTRONG and WILSON 1964 (547) 180, 166
ARNOLD 1965 (S 307) 345
ARONOW 1971 (713) 235, 220
ARONOW and ROKAW 1971 (1050) 305, 301
ARONOW and SWANSON 1969 (40) 25, 21
ARONOW and SWANSON 1969 (781) 242, 240
ARONOW, DENDINGER and ROKAW 1971 (1048) 305, 301
ARONOW, KAPLAN and JACOB 1968 (39) 25, 21, 402 (a)
ARONOW, HARRIS, ISBELL, ROKAW and IMPARTO 1972 (1049) 305, 301
ARTURSON, GARBY, ROBERT and ZAAR 1972 (987) 293, 292
ASANO and BRANEMARK 1970 (782) 242, 241
ASHBY, DALBY and MILLAR 1965 (845) 251, 250
ASHER 1968 (S 151) 333
ASKANSAS, LISZEWSKA and TYLKA 1970 (A 295) 119

483

1005050843

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

ASSMUSSEN and PAULSEN 1953 (1051) 305, 303
ASSMUSSEN and VINTHER-PAULSEN 1949 (1128) 318, 316
ASSMANN 1939 (A 723) 260
ASTRUP 1964 (101) 65, 63
ASTRUP 1964 (1084) 311, 308
ASTRUP 1966a (1085) 311, 308
ASTRUP 1966b (1086) 311, 308
ASTRUP 1967 (1087) 311, 309
ASTRUP 1969 (1088) 311, 309
ASTRUP 1970 (1089) 311, 309
ASTRUP 1972 (1090) 311, 309
ASTRUP, KJELDSEN and WANSTRUP 1967 (1092) 311, 309
ASTRUP, KJELDSEN and WANSTRUP 1970 (1094) 311, 309
ASTRUP, KJELDSEN and WANSTRUP 1970 (1093) 311, 309
ASTRUP, HELLUNG-LARSEN, KJELDSEN and MELLEMGAARD 1966 (1091) 311, 308
ASTRUP, PAULI, KJELDSEN and PETERSEN 1968 (1095) 311, 309
ATHEROSCLEROSIS STUDY GROUP 1970 (A 418) 145
AUERBACH, HAMMOND and GARFINKEL 1965 (80) 58, 466 (a)
AUERBACH, HAMMOND, GARFINKEL and KIRMAN 1971 (715) 235, 233
AUERBACH, HAMMOND, KIRMAN and GARFINKEL 1967 (714) 235, 233
AUSTRALIAN NATIONAL HEART FOUNDATION 1971 (A 419) 145
AVIADO 1972 (863) 267, 264
AVIADO, SAMANEK and FOLLE 1966 (862) 267, 266, 365 (a)
AYERS, GIANELLI and ARMSTRONG 1965 (988) 293, 291
AYRES, GIANELLI and ARMSTRONG 1965 (1052) 305, 302
AYRES, GIANELLI and MUELLER 1970 (1053) 305, 301
AYRES, MUELLER, GREGORY, GIANELLI and PENNY 1969 (1054) 305, 301
BAER 1966 (371) 133, 132
BAGWELL, WOODS and RICHARDSON 1960 (A 692) 257
BAHL, BASU and CHUGH 1970 (335) 124, 123, 122
BAHRMANN 1970 (A 296) 119
BAILEY, HABERMAN and SHEINBERG 1969 (273) 99, 98
BALBO, MARUCCI and RONCHI 1966 (989) 293, 289
BALESTRA and CANEPA 1967 (648) 211, 210
BALL 1970 (S 157) 334
BALL 1972 (S 122) 331
BALL 1972 (S 170) 334
BALL, KIRBY and BOGEN 1965 (A 626) 225
BALOTIN 1959 (A 63) 29
BALOURDAS 1966 (933) 276, 275
BALOW, ALTER and RESCH 1966 (157) 72, 71
BALTZAN 1939 (A 627) 225
BANERJEA 1967 (A 279) 118
BANKS, RAFTERY and ORAM 1971 (41) 25, 23
BANKS, RAFTERY and ORAM 1971 (81) 58, 55
BANSAL, CHABLANI and GULATI 1970 (554) 180, 166
BARACH, ECKMAN and MOLOMUT 1941 (1018) 298, 296
BARBANO, BAROCELLI and DE MATTEIS 1954 (A 514) 192
BARBORIAK, RIMM, TRISTANI, WALKER and LEPLEY 1972 (A 64) 29
BARGERON, EHMKE, GONLUBOL, CASTELLANOS, SIEGEL and BING 1957 (716) 235, 230
BARNETT and BOAKE 1960 (784) 242, 241
BARRON 1968 (214) 92, 90
BARRON 1948 (A 65) 29
BARTHE, PARIS, DUCHEMIN and THOMAS 1953 (990) 293, 290
BARTLETT 1968 (1129) 318, 315
BASSETT 1962 (A 556) 196
BASSETT, MOELLERING, ROSENBLATT, GREENBERG and STOKES 1969 (470) 172, 162
BASSETT, ABEL, MOELLERING, ROSENBLATT and STOKES 1969 (472) 172, 162
BASSETT, ABEL, MOELLERING, ROSENBLATT and STOKES 1969 (469) 172, 162
BASSETT and SCHROFFNER 1970 (473) 172, 162
BASTIDE and HOUDAILLE 1971 (A 481) 190
BEADENKOPF, ABRAMS, DAOUD and MARKS 1963 (274) 99, 97, 96
BEARD 1963 (A 229) 102
BEAU 1862 (3) 19, 15
BEAU 1863 (4) 19, 15
BECKETT and TRIGGS 1967 (864) 267, 264
BEGG 1965 (102) 65, 62
BEGG 1972 (A 141) 49
BELL 1970 (S 308) 345
BELLET, DeGUZMAN, KOSTIS, ROMAN and FLEISCHMANN 1972a (718) 235, 233
BELLET, HORSTMANN, ROMAN, DeGUZMAN and KOSTIS 1972b (719) 235, 23

1005050844

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

BELLET, KERSHBAUM, MEADE and SCHWARTZ 1941 (717) 235, 232
BELLET and ROMAN 1969 (A 242) 116
BELLET, WEST and GUZMAN 1960a, (899) 272, 270
BELLET, WEST, MANZOLI, MULLER and ROSSI 1960b (900) 272, 271
BELLI, ALBERTINI, MARTINESI and PELLEGRINI 1965 (972) 284, 283
BELLI and GUILIANO 1955 (1019) 298, 296
BENNETT, DOLL and HOWELL 1970 (422) 155, 154
BENNETT 1972 (S 217) 338
BENSON, COSTAS, GARCIA-PALMIERI, FELIBERTI, AIXLA, BLANTON and COLON 1966 (596) 184, 169, 361 (a)
BERG and MELKILD 1962 (591) 183, 169
BERGEL and MAKIN 1966 (865) 265
BERGEL and MAKIN 1967 (866) 266, 265
BERGMAN, VAN DER LINDEN and SODERSTROM 1968 (72) 44, 43
BERKSON, STAMLER and JACKSON 1966 (403) 150, 149
BERKSON, STAMLER, LINDBERG, MILLER, MATHIES, LASKY and HALL 1960 (215) 92, 90
BERKSON 1960 (S 309) 1960
BERMAN 1969 (A 331) 139
BERRY 1960 (A 117) 47
BERRY 1960 (51) 35, 34
BERTRAND, AYE, BEDA, BARABE, LEBRAS and DELLOUE 1971 (590) 183, 169
BEST, JOSIE and WALKER 1961 (504) 176, 164
BEST and WALKER 1964 (505) 177, 164
BEST, WALKER, BAKER, DELAQUIS, McGREGOR and McKENZIE 1967 (506) 177, 164
BESTERMAN, MYAT and TRAVADI 1967 (973) 284, 282
BETHLENFALVAY 1971a (1130) 318, 316
BETHLENFALVAY 1971b (1131) 318, 316
BETTMAN, FELLOWS and CHAO 1958 (783) 242, 241
BEVILACQUA 1965 (A 178) 52
BHAGAT 1968 (934) 276, 275
BHAGAT, BOVELL and ROBINSON 1967 (A 693) 257
BHAGAT, ROBINSON and WEST 1967 (A 664) 255
BHAGAT, RUEHL, RAO, RANA and HUGHES 1971 (935) 276, 275
BHOWN, MAITRYA and HAQ 1969 (991) 293, 291
BICKENBACH and SOOST 1966 (A 34) 27
BIENER 1967 (S 88) 329
BIERENBAUM, FLEISCHMAN, GREEN, RAICHELSON, HAYTON, WATSON and CALDWELL 1970 (A 420) 145
BINET and BURNSTEIN 1948 (1096) 311, 308
BING, BENNISH, BLUEMCHEN, COHEN, GALLAGHER and ZALESKI 1964 (A 21) 14
BING, WAYLAND, RICKART and HELLBE 1971 (901) 272, 270
BIORCK 1964 (A 531) 193
BIORCK 1964 (A 330) 139
BIORCK 1965 (A 532) 193
BIRNSTINGL, BRINSON and CHAKRABART 1971 (1132) 318, 315
BIRNSTINGL, COLE and HAWKINS 1966 (1097) 311
BIRNSTINGL, COLE and HAWKINS 1967 (1133) 318, 316, 389 (a)
BIRNSTINGL, COLE and HAWKINS 1967 (103) 66, 63
BISCARDI and WASSERMANN 1966 (A 694) 257
BLACKBURN, BROZEK and TAYLOR 1960 (631) 205, 204
BLACKBURN, BROZEK, TAYLOR and KEYS 1960 (S 67) 328
BLACKBURN, KEYS, KARVONEN, VAN BUCHEM and TAYLOR 1967 (A 393) 143, 379 (a)
BLACKBURN, ORMA, HARTEL and PUNSAR 1959 (859) 252, 250
BLACKBURN, PARLIN and KEYS 1967 (A 537) 194
BLACKMORE 1970 (1134) 318, 316
BLAKE 1964 (S 71) 328
BLACKET 1971 (S 161) 334
BLANC 1925 (5) 19, 18
BLASCHKO, HAGEN and WELCH 1955 (A 695) 257
BLOHMKE, SCHAEFER, ABEL, DEPNER, GRUNTZIG, KOSCHORRECK and STELZER 1969 (A 558) 196
BLOMSTRAND and LUNDMAN 1966 (S 85) 329
BLOMSTRAND and LUNDMAN 1966 (A 557) 196
BLOOM 1966 (A 332) 139
BLUE 1970 (104) 65
BLUMCHEN, KIEFER, ROSKAMM, WALDMANN, BUCHNER and REINDELL 1969 (A 485) 190
BLUMER 1934 (S 125) 332
BLUMER 1934 (52) 35, 34
BOAS and LEVY 1936 (619) 203, 201

10050845

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

BOEK and BOEK 1963 (A 559) 196
BOELLING, PHILLIPS, FRERKING and PAINE 1967 (A 394) 143
BOLENS and FERRERO 1967 (336) 124, 123
BOLETIN DE LA ASSOCIATION MEDICA DE PUERTO RICO 1967 (S 237) 340
BOLLINGER 1971 (A 665) 255
BOLLINGER, LICHTLEN, KAINDL and MANNHEIMER 1972 (105) 65, 63
BORCHGREVINK, BJERKELUND, ABRAHAMSEN, BAY, BORGEN, GRANDE, HELLE, KJORSTAD, PETERSEN, RORVIK, THORNSEN and ODEGAARD 1968 (A 597) 199
BORDEN and IBRAHIM 1970 (620) 203, 201
BORHANI and HECHTER 1964 (632) 205, 204
BORHANI, HECHTER and BRESLOW 1963 (216) 92, 91
BOROJEV and STANULOVIC 1971 (610) 185, 170
BOSE 1970 (A 421) 145
BOSE 1971 (S 113) 331
BOUDIK 1971 (A 466) 188
BOURKE (S 310) 345
BOWDEN and WOODHALL 1964 (1020) 298, 297
BOYER 1942 (A 545) 195
BOYLE 1968 (A 280) 118
BOYLE, MORALES, NICHAMAN, TALBERT and WATKINS 1968 (815) 248, 246
BOYLE, WEGRIA, CATHCART, NICKERSON and LEVY 1947 (902) 272, 271
BRACHFELD, BOZER and GORLIN 1959 (A 22) 14
BRACHFELD, KUEHN, KAWADE and ORAN 1967 (868) 265,
BRACHFELD and ORAN 1966 (867) 265
BRAKMAN, ALBRECHTSEN and ASTRUP 1967 (690) 218, 216
BRANDT, JONES and MATHER 1967 (A 66) 29
BRASS 1970 (S 311) 345
BRAUNSTEINER, SANDHOFER and SAILER 1969 (A 118) 47
BRAUNWALD, CHIDSEY, HARRISON, GAFFNEY and KAHLER 1963 (A 696) 257
BRAY and McDONALD 1966 (A 598) 199
BRESLOW and BUELL 1960 (A 395) 143
BREST 1964 (A 333) 139
BRETT 1968 (550) 180, 166
BREWER, EATON and GROVER 1970 (1136) 318, 315
BREWER, EATON, WEIL and GROVER 1970 (992) 293, 291
BREWER, EATON, GROVER and WEIL 1971 (993) 293, 291
BREWER, EATON, GROVER and WEIL 1971 (1135) 318, 315
BRIEMEISTER 1943 (S 18) 324
BRIGDEN 1958 (A 1) 12
BRIGMAN 1921 (S 11) 324
BRIGHTMAN 1965 (A 334) 139
BRINKMAN 1962 (A 724) 260
BRITISH BROADCASTING COMPANY 1969 (A 96) 31
BRITISH HEART JOURNAL 1969 (S 281) 343
BRITISH MEDICAL JOURNAL 1955 (S 218) 339
BRITISH MEDICAL JOURNAL 1956 (S 219) 339
BRITISH MEDICAL JOURNAL 1963 (S 221) 339
BRITISH MEDICAL JOURNAL 1963 (S 220) 339
BRITISH MEDICAL JOURNAL 1964 (S 226) 339
BRITISH MEDICAL JOURNAL 1964 (S 72) 328
BRITISH MEDICAL JOURNAL 1964 (S 225) 339
BRITISH MEDICAL JOURNAL 1964 (S 224) 339
BRITISH MEDICAL JOURNAL 1966 (S 234) 339
BRITISH MEDICAL JOURNAL 1966 (S 235) 339
BRITISH MEDICAL JOURNAL 1968 (S 276) 342
BRITISH MEDICAL JOURNAL 1969 (S 245) 340
BRITISH MEDICAL JOURNAL 1969 (S 282) 343
BRITISH MEDICAL JOURNAL 1969 (S 244) 340
BRITISH MEDICAL JOURNAL 1970 (S 288) 343
BRITISH MEDICAL JOURNAL 1971 (S 257) 341
BRITISH MEDICAL JOURNAL 1971 (S 256) 341
BRITISH MEDICAL JOURNAL 1971 (S 255) 341
BRITISH MEDICAL JOURNAL 1972 (S 263) 341
BRITISH MEDICAL JOURNAL 1972 (S 262) 341
BRITMAN and LEVINE 1964 (A 725) 260
BRODY and COBURN 1969 (1137) 318, 316
BRODY and COBURN 1970 (1056) 305, 302
BRODY and COBURN 1969 (1055) 305, 302
BRONTE-STEWART 1960 (S 31) 325
BRONTE-STEWART 1961 (597) 184, 169
BRONTE-STEWART 1961 (S 34) 325
BRONTE-STEWART, KEYS, BROCK, MOODIE, KEYS and ANTONIS 1955 (649) 211, 207
BROOKS 1915 (6) 19, 18, 15
BROWN 1962 (542) 179, 166
BROWN 1896 (7) 19, 15

1005050846

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

BROWN, SELLWOOD, HARRISON and MARTIN 1969 (A 179) 52
BROWN 1972 (S 312) 345
BROWN and RITZMAN 1967 (372) 133, 129
BROWN, McKEOWN and WHITFIELD 1957 (537) 179, 166
BROWNLEE 1965 (S 313) 345, 353 (a)
BRUCE 1901 (8) 19, 15
BRUGGEMANN 1969 (A 349) 140
BRUHN and WOLF 1970 (373) 133, 129
BRUHN, WOLF, LYNN, BIRD and CHANDLER 1968 (495) 175, 163
BRUNNER and MANELIS 1960 (567) 181, 167
BRUNTON 1905 (S 7) 323
BRUNTON 1906 (S 8) 323
BRYANT and WOOD 1947 (9) 19, 17
BUCHANAN 1969 (720) 235, 230
BUECHLEY, DRAKE and BRESLOW 1958 (217) 92, 91
BUFFONI and GIOTTI 1961 (A 666) 255
BUINEWITSCH 1940 (10) 19, 18
BULL 1969 (A 199) 54
BULLETIN OF THE LOS ANGELES CITY MEDICAL ASSOCIATION 1968 (S 277) 342
BULLETIN OF THE LOS ANGELES CITY MEDICAL ASSOCIATION 1968 (S 278) 342
BUNN and JANDL 1970 (1138) 318, 315
BURCH 1949 (A 67) 29
BURCH 1972 416(j)
BURCH 1972 424(a)
BURCH and DePASQUALE 1962 (704) 221, 219
BURCH and DePASQUALE 1965 (A 35) 27
BURCH and DePASQUALE 1965 (A 23) 14
BURCH and DePASQUALE 1966 (A 97) 31
BURCH and ROWELL 1966 (S 147) 333, 368 (b)
BUREAU 1907 (11) 19, 15
BURN 1951 (A 697) 257
BURN 1960 (A 667) 255
BURN and GIBBONS 1965 (A 698) 257
BURN, LEACH, RAND and THOMPSON 1959 (A 668) 255
BURN and RAND 1958 (A 669) 255, 426 (a)
BURNEY and ENSLEIN 1972 (650) 211, 209
BURNS-COX, CHONG and GILLMAN 1972 (A 524) 193
BURNS-COX, DOLL and BALL 1969 (423) 155, 154
BURT 1960 (A 560) 196
BUTKUS and PAGE 1965 (816) 248, 246
BUXTORF and BEAUMONT 1968 (721) 235, 228
BUYTENDIJK and MAESEN 1964 (73) 44, 43
BYGDEMAN, ELIASSON and JOHNSON 1966 (A 599) 199
BYGDEMAN and EULER 1958 (A 699) 257
BYRD, DIVERTIE and SPITTELL 1967 (A 600) 199
BUZINA, KEYS, MOHACEK, HAHN, BROZEK and BLACKBURN 1967 (614) 185, 170
CAFFERY 1967 (A 297) 119
CAMPBELL 1963a (275) 99, 97
CAMPBELL 1963b (276) 99, 97
CAMPOS and DELNERI 1969 (578) 182, 168
CANADIAN DEPARTMENT OF NATIONAL HEALTH AND WELFARE 1966 (507) 177, 164
CANADIAN DEPARTMENT OF NATIONAL HEALTH AND WELFARE 1966 (508) 177, 164
CANADIAN DEPARTMENT OF NATIONAL HEALTH AND WELFARE 1966 (509) 177, 164
CANADIAN MEDICAL ASSOCIATION JOURNA 1964 (S 227) 339
CANADIAN MEDICAL ASSOCIATION JOURNA 1970 (S 289) 343
CANADIAN MEDICAL ASSOCIATION JOURNA 1972 (S 264) 341
CANDURA and CRAVERIA 1964 (1139) 318, 315
CANEPA, BALESTRA and BUCCELLI 1968 (579) 182, 168
CANNON and GRAY 1914 (974) 284, 282
CANNON and MENDENHALL 1914a (975) 284, 282
CANNON and MENDENHALL 1914b (976) 284, 282
CARLSON and BOTTIGER 1972 (651) 211, 210
CARRUTHERS 1969 (A 298) 119
CARRUTHERS 1964 (S 194) 336
CARTER 1969 (S 208) 337
CARVER 1971 (A 150) 50
CASCIU, MARRACCINI, ZEDDA, CARTA and FULGHESU 1968 (575) 182, 168
CASE 1958 (455) 171, 161
CASPER 1932 (74) 44, 43
CASSEL 1971 (218) 92, 89
CASSEL 1971 (219) 92, 89
CASSEL, HEYDEN, BARTEL, KAPLAN, TYROLER, CORNONI and HAMES 1971 (374) 133, 130, 473 (a)
CASSIDY 1946 (A 151) 50
CASTELLINO 1955 (1021) 298, 296
CATHEY, JONES, NAUGHTON, HAMMARSTEN and WOLF 1962 (A 561) 196
CEDERLOF 1966c (311) 109, 107
CEDERLOF and EDFORS 1968 (869) 265, 264

1005050847

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

CEDERLOF and JOHNSSON 1967 (312) 109, 107
CEDERLOF, FLODERUS and FRIBERG 1970 (313) 109, 108
CEDERLOF, FRIBERG and HRUBEC 1969 (315) 109, 108
CEDERLOF, FRIBERG and LUNDMAN 1968 (A 2) 12
CEDERLOF, JONSSON and LUNDMAN 1966a (309) 109, 107
CEDERLOF, EDFORS, FRIBERG and JONSSON 1967 (314) 109, 108
CEDERLOF, FRIBERG, JONSSON and KALI 1966b (310) 109, 107, 364 (a)
CHAPMAN 1967 (S 89) 329
CHAPMAN 1892 (S 5) 323
CHAPMAN, GOERKE, DIXON, LOVELAND and PHILLIPS 1957 (463) 171, 162
CHAPPELL, GARROD, JONES, ROLFE and WESOLKOWSKI 1970 (A 628) 225
CHARMS 1968 (A 3) 12
CHARTERS and ARYA 1960 (S 131) 332
CHATTOPADHAYA, MITTAL, BHARGAVA and SHARMA 1968 (562) 181, 167
CHEDD and STUBBS 1961 (S 314) 345
CHERASKIN and RINGSDORF 1971 (456) 171, 160
CHERRY and FORBES 1972 (S 171) 334, 424 (b)
CHEVALIER, KRUMHOLZ and ROSS 1963 (1057) 305, 302, 362 (a)
CHEVALIER, BOWERS, BONDURANT and ROSS 1963 (722) 235, 231, 367 (a)
CHIANG and LEADERS 1966 (A 670) 255
CHIANG and LEADERS 1968 (A 671) 255
CHIANG, PERLMAN, OSTRANDER and EPSTEIN 1969 (221) 92, 90
CHIANG, ALEXANDER, BRUCE, THOMPSON and TING 1969 (A 396) 143
CHIANG, PERLMAN, FULTON, OSTRANDER and EPSTEIN 1970 (220) 92, 90
CHIARI 1938 (A 36) 27
CHIDSEY, BRAUNWALD and MORROW 1965 (A 726) 260
CHIDSEY, SONNENBLICK, MORROW and BRAUNWALD 1966 (A 727) 260
CHIEF MEDICAL OFFICER OF THE MINISTRY OF HEALTH 1968 (S 92) 330
CHRISTAKIS, RINZLER, ARCHER and KRAUS 1966 (A 424) 145
CHRISTAKIS, RINZLER, ARCHER, HASHIM and VAN ITALLIE 1965 (A 422) 145
CHRISTAKIS, RINZLER, ARCHER, WINSLOW JAMPEL, STEPHENSON, FRIEDMAN FEIN, KRAUS and JAMES 1966 (A 423) 145
CHRISTIAN 1968 (A 299) 119
CHRISTIE 1971 (A 454) 188
CHRISTMANN 1969 (A 37) 27
CHUNG, BASSETT, MOELLERING, ROSENBLATT, STOKES and YOSHIZAKI 1969 (471) 172, 162
CIAMPOLINI, DRINGOLI and RAVAIOLI 1968 (817) 248, 246.
CICALA, D'ONOFRIO and BARONE 1967 (A 425) 145
CIRCULATION 1970 (S 250) 340
CISWICKA-SZNAJDERMAN, SZNAJDERMAN JANUSZEWICZ, DZIERZYKRAY-ROGALSKI, PROMINSKA and CHARZEWSKI 1971 (337) 124, 123
CLANCY, GRAHAM, POWELL and GILMOR 1967 (A 728) 260
CLARK, CHAPMAN and COULSON 1967 (633) 205, 204
CLEAVE 1971 (S 162) 334
CLEMENTE and MARCHIONNI 1969 (A 515) 192
CLEMMESEN 1969 (A 526) 193
CLOAREC (A 243) 116
COFFIN 1956 (S 27) 325
COFFMAN and JAVETT 1963 (785) 242, 24
COHEN 1969 (652) 211, 207
COHEN and SHAFRIR 1965 (424) 155, 153
COHEN and THOMAS 1962 (705) 221, 220
COHEN and HEIMANN 1962 (277) 99, 98
COHEN and HEIMANN 1962 (S 315) 345, 352
COHEN, DEANE and GOLDSMITH 1969 (1058) 305, 300
COHEN, LUEBS, ZALESKI and BING 1966 (A 24) 14
COHEN, ZALESKI, LUEBS and BING 1965 (A 25) 14
COHEN, PERKINS, URY and GOLDSMITH 1971 (1022) 298, 295
COLE, SINGIAN and KATZ 1954 (65) 42, 39
COMROE 1960 (A 749) 262
COMSTOCK 1971 476(a)
CONN and KISSANE 1958 (A 68) 29
CONNALLY 1969 (A 281) 118
CONNOR, HOAK and WARNER 1963 (A 601) 199
CONSTOCK 1971 (480) 173, 162
COOKE 1964 (S 196) 336
COOPER 1969 (A 335) 139
COOPER 1972 (A 119) 47
COOPER and MITCHELL 1969 (A 120) 47
COOPER, GEY and BOTTENBERG 1968 (404) 150, 149
CORBASCIO and WEST 1960 (903) 272, 271
CORELLI 1966 (106) 66, 61
CORET and HUGHES 1964 (1098) 312, 308
CORNFIELD 1970 (A 213) 77
CORNFIELD and HAENSZEL 1960 (A 214) 77

1005050848

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CORNFELD and MITCHELL 1969 (278) 99, 98
CORNWALL 1934 (12) 19, 15
CORONARY DRUG PROJECT RESEARCH GROUP 1969 (66) 42, 39
CORONARY DRUG PROJECT RESEARCH GROUP 1970 (653) 211, 207
CORSINI, PURI and BING 1968 (904) 272, 271
COSCIA, PERRELLI, GAIDO and CAPELLARO 1964 (1140) 318, 315
COTTON, NIXON, CARPENTER and EVANS 1972 (552) 180, 166
COUGHLIN 1902 (S 6) 323
COX 1967 (67) 42, 40
CRAMER 1965 (S 44) 326
CRAMER, PAULIN and WERKO 1966 (654) 211, 208
CRECELIUS, STRAUZENBERG and POKLEKOWSKI 1966 (535) 174, 165
CREUX, HARTMANN, WIDMER, GREENSHER, BREIL, REBER, STAUB and KAUFMANN 1963 (A 562) 196
CROOG, SHAPIRO and LEVINE 1971 (A 629) 225
CROSETTI, RUBINO and PETTINATI 1966 (1023) 298, 296
CULLEN 1972 (499) 176, 164
CURPHEY, HOOD and PERKINS 1965 (994) 293, 289
CUTTS 1965 (A 98) 31
DAHLSTROM, NORDSTROM-OHRBERG and ROTHSCHILD 1958 (995) 293, 290
DALDERUP 1971 (S 163) 334
DALDERUP 1971 (587) 183, 168
DALDERUP 1973 (S 180) 335
DALDERUP, STOCKMAN, RECHSTEINER, and VAN DER SILKKE 1965 (586) 182, 168
DALE 1963 (870) 265, 264
DAMON 1961 (375) 133, 131
D'ANTUONO and COCCHERI 1968 (A 602) 199
DAWBER 1963 (174) 85, 82, 81
DAWBER 1969 (A 244) 116
DAWBER and KANNEL 1961 (A 245) 116
DAWBER and KANNEL 1962a (175) 85, 81
DAWBER and KANNEL 1962b (176) 85, 81
DAWBER and KANNEL 1962 (A 216) 77
DAWBER, KANNEL and LYELL 1963a (177) 85, 82
DAWBER, KANNEL and FRIEDMAN 1963b (178) 85, 82
DAWBER, KANNEL, McNAMARA 1963 (179) 85, 81
DAWBER, KANNEL, REVOTSKIE and KAGAN 1962 (181) 85, 81
DAWBER, KANNEL, REVOTSKIE, STOKES KAGAN and GORDON 1959 (182) 85, 81
DAWBER, MOORE and MANN 1957 (180) 85, 80
DAWBER and THOMAS 1968 (A 142) 49
DAWBER and THOMAS 1969 (A 246) 116
DAWBER and THOMAS 1971 (A 336) 139
DAVIDSON, BRAAK, PRESTON and JUDGE 1972 (A 69) 29
DAVIGNON 1963 (A 215) 77
DAVIS 1959 (725) 236, 231
DAVIS, SCARBOROUGH, MASON, SINGEWALD and BAKER 1953 (723) 235, 231
DAVIS, SCARBOROUGH, MASON, SINGEWALD and BAKER 1956 (724) 235, 229
DAYTON 1971 (655) 211, 207
DAYTON, CHAPMAN, PEARCE, POPJAK 1970 (A 200) 54
DAYTON and PEARCE 1969 (A 246) 145
DAYTON and PEARCE 1970 (S 158) 334, 41
DAYTON, PEARCE, HASHIMOTO, DIXON and TOMIYASU 1969 (445) 159, 157
DeBIAS, BIRKHEAD, BANERJEA, KAZAL HOLBURN, GREENE, HARPER, ROSEFELD, MENDUKE, WILLIAMS and FRIEDMAN 1972 (1059) 305, 301
DeBRAY, CHRETIEN, GUENIOT, HARDOLIN HIMBERT, PICHOT, RICHET, ROUSSE and RYCKEWAERT 1969 (A 337) 139
DEC 1960 (726) 236, 229
DECAISNE 1879 (S 1) 323
DE CRINIS, REDISCH, FONTANA, LEWIS, SULZBERGER and STEELE 1960 (107) 66, 62
DE LA CHAPELLE and CONNOR 1964 (A 99) 31
DELAHAYE, BESSET and TOUBOUL 1970 (108) 66, 65
DELARUE 1962 (S 37) 326
DELEIXHE, and REGINSTER-HANEUSE 1970 (502) 176, 164
DELLA SALDA, TURINA and CUIDUCCI 196 (571) 181, 167
DELUCA, PIANCONE, D'ADDETTA, CRAMA ROSSA, ADNREOLI and NEGRI 1968 (A 38) 27
DE MOLO 1970 (581) 182, 168
DENHAM 1969 (S 155) 333
DE SOLDATI, BARBIERO, CHUTLIAN, ROSENTAL and MATTIAUDA 1971 (497) 176, 164
DE SOLDATI, BARBIERO, CHUTLIAN, (68) 42, 39
DEWAR 1971 (657) 211, 209
DEWAR 1972 (656) 211, 207
DHALLA 1967 (A 672) 255
DHALLA and LcLAIN 1966 (A 673) 255

10050849

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

DIAMANT-BERGER, GAJDOS, RAPIN and GOULON 1970 (1060) 306, 302
DI CONTOGNO, VIZZERI, ORIONE and GALASSO 1968 (576) 182, 168
DIEHL 1969 (S 209) 337
DIEHL 1970 (S 108) 330
DIMOND 1964 (386) 136, 134
DINMAN 1969 (1061) 306, 300
DINTENFASS 1969 (706) 221, 219
DISEASE OF THE CHEST 1968 (S 279) 342
DJORDJEVIC, BALOC, BOZINOVIC, JOSIPOVIC, NEDELJKOVIC, LAMBIC, SEKULIC, SLAVKOVIC, STOJANOVIC, SIMIC, SIMIC, STRASSER, BLACKBURN and KEYS 1970 (615) 185, 170
DJORDJEVIC, JOSIPOVIC, NEDELKOVIC, STRASER, SLAVKOVIC, SIMIC, KEYS and BLACKBURN 1967 (613) 185, 170
DLIN 1969 (S 104) 330
DOCK 1959 (A 152) 50
DOCK 1963 (905) 272, 271
DOCK 1963 (S 191) 336
DODGE 1971 (A 729) 260
DOERKEN 1968 (338) 124, 123
DOLL 1972 416(k)
DOLL and HILL 1954 (299) 106, 103
DOLL and HILL 1956 (298) 106, 103
DOLL and HILL 1964a (296) 106, 103
DOLL and HILL 1964b (297) 106, 103
DOLL and HILL 1966 (300) 106, 103, 359(a)
DOMINO 1967 (A 750) 262
DONTENWILL, RECKZEH and STADLER 1966 (1024) 298, 296
DONTENWILL, RECKZEH and STADLER 1967 (1025) 298, 296
DORKEN 1967 (339) 124, 123
DORKEN 1967 (357) 128, 127, 126
DORKEN 1972 (A 486) 190
DORMANDY 1965 (S 143) 333
DORMANNS and EMMINGER 1934 (75) 44, 43
DORN 1958 (183) 85, 80
DORN 1959 (184) 85, 80
DOUGLAS 1970 (A 121) 47
DOUGLAS and ARKUN 1969 (316) 109, 108
DOWER and OSBORNE 1972 (621) 203, 202
DOYLE 1964 (S 40) 326
DOYLE 1966 (A 122) 47
DOYLE 1966 (A 247) 116
DOYLE 1968 (S 50) 327
DOYLE 1968 (S 49) 326
DOYLE 1969 (A 339) 139
DOYLE 1969 (S 55) 327
DOYLE 1969 (A 338) 159
DOYLE 1969 (S 105) 330
DOYLE, DAWBER, KANNEL, HESLIN and KAHN 1964 (224) 92, 89
DOYLE, HESLIN, HILLEBOE and FORMEL 1959 (222) 92, 89
DOYLE and KINCH 1970 (622) 203, 201
DOYLE, KINCH and BROWN 1968 (485) 174
DRAKE and BUECHELLI and BRESLOW 195 (225) 92, 91
DRASH 1972 (A 553) 196
DREXLER 1968 (109) 65, 64
DRISCOLL, DEUBER, BAETTIG and GRANDJEAN 1972 (1026) 298, 296
DuBOIS 1970 (1141) 318, 315
DUERFELDT 1945 (13) 19, 18
DUGGAN, SCHIESS and HILFINGER 1971 (A 39) 27
DUNCAN 1967 (A 340) 139
DUNCAN and BEST 1969 (A 341) 139
DUNGAL and BENEDIKTSSON 1958 (76) 44, 43
DWYAR, WIENER and COX 1969 (A 26) 14
DYKEN 1970 (158) 72, 70
EADES 1969 (A 123) 47
EASTCOTT 1962 (110) 66, 65
EASTCOTT 1971 (A 180) 52
EASTWOOD and TREVELYAN 1971 (A 30) 119
ECCLES and LIBET 1961 (A 674) 255
EDITORIAL 1968 (A 342) 139
EDITORIAL 1968 (A 248) 116
EDITORIAL 1968 (A 243) 139
EDITORIAL 1971 (42) 25, 24
EDMUNDOWICZ, CIPOLLONI and PENROD 1965 (728) 236, 233, 386 (a)
EDMUNDOWICZ, PIFER and MARSHALL 1964 (727) 236, 230
EDWARDS, MCKEOWN and WHITFIELD 1959 (634) 205, 204
EDWARDS, McKEOWN and WHITFIELD 1959 (538) 179, 166, 445 (b)
EILERTSEN and SULHEIM 1970 (A 4) 12
EISEN 1966 (111) 66, 63
EISEN, and HAMMOND 1956 (A 47) 251, 250
EISEN and HAMMOND 1956 (1142) 319, 316
EL-ATTAR 1968a (1143) 319, 315
EL-ATTAR 1968b (1144) 319, 315
EL-DIA MEDICO 1967 (S 275) 342
EL-DIA MEDICO 1969 (S 283) 343
EL-EBRASHY, EL-ASHMAWY and ALY 1967 (846) 251, 250
EL-EBRASHY, EL-ASHMAWY and ALY 1967 (1145) 319, 315
ELIOT and BRATT 1969 (1146) 319, 317
ELIOT and MIZUKAMI 1966 (1147) 319, 315
ELKELES 1973 (S 181) 335
ELLIOT, STEWART, OCHOA, WEST and BOOKER 1968 (A 675) 255

1005050850

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

ELLIS and MONTEGRIFFO 1970 (A 247) 145
ELWOOD, WATERS, MOORE and SWEETNAM 1970 (425) 155, 154
EMMERICH 1970 (A 41) 27
EMMONS, HARRISON, HONOUR and MITCHELL 1965 (A 603) 199
EMMRICH and REINDELL (A 40) 27
ENGELBARG 1965 (848) 251, 250
ENGELBERG and ENGELBERG 1968 (851) 251, 250
ENGELBERG and FUTTERMAN 1966 (849) 251, 250
ENGELBERG and FUTTERMAN 1967 (850) 251, 250
ENTICKNAP, GOODING, LANSLEY and AVIS 1969 (A 604) 199
ENZI 1969 (A 282) 118
EPIDEMIOLOGY COMMITTEE OF THE SECOND ANNUAL CONFERENCE ON CARDIOVASCULAR DISEASE (A 564) 196
EPSTEIN 1965 (279) 99, 98
EPSTEIN 1966 (A 217) 77
EPSTEIN 1967 (A 218) 77
EPSTEIN 1967 (426) 155, 153
EPSTEIN 1967 (226) 92, 90
EPSTEIN 1968 (A 219) 77
EPSTEIN 1969 (427) 155, 153
EPSTEIN 1971 (A 230) 102
EPSTEIN 1971 (A 124) 47
EPSTEIN, OSTRANDER, JOHNSON, PAYNE, HAYNER, KELLER and FRANCIS 1965 (227) 92, 90
ERIBANI, CONSTANTINO and PORRO 1967 (A 70) 29
ERNSTENI 1963 (A 344) 139
ESPEJO SOLO 1936 (A 630) 225
ESPINER, TUCCI, JAGGER and LAULER 1967 (A 546) 195
ESTANDIA CANO, RSQUIVEL AVILA, MALO CAMACHO, FEREZSANTANDER, LEON MONTANAZ 1971 (341) 124, 123
EYSENCK, TARRANT, WOOLF and ENGLAND 1960 (387) 136, 134
FABRE, TRUHAUT and BERROD 1951 (1027) 298, 297
FACCHINI, SEMARARO, DI BIASE, TABARRONI, SPAGNOLO, AUTORE and BONAVITA 1971 (852) 251, 250
FALK 1947 (A 72) 29
FALK 1947 (A 71) 29
FALSETTI, SCHNATZ, GREENE and BUNNELL 1970 (A 565) 196
FARBER 1965 (S 79) 329
FAVARGER 1887 (S 4) 323
FAWAZ 1963 (A 700) 257
FEJFAR 1969 (A 345) 140
FEJFAR 1972 (A 249) 116
FEJFAR and PISA 1970 (A 250) 116
FEJFAR and PISA 1971 (A 100) 31
FEJFAR and VANECEK 1970 (A 346) 140
FEJGIN 1966 (A 73) 29
FELTON 1968 (A 201) 54
FERREIRA, ANDERIZ, FIGUERA and CEBOLLADA 1968 (A 730) 260
FERUGLIO and CAMERINI 1968 (A 516) 192
FETCHER 1969 (A 428) 145
FIDANZA, IMBIMBO and DI BENEDETTA 1966 (A 517) 192
FIDANZA, PUDDU, VECCHIO and KEYS 1967 (572) 181, 168
FIEGEL 1969 (A 283) 118
FIESER 1966 (A 631) 225
FIESSINGER 1913 (S 316) 346
FIESSINGER 1919 (A 632) 225
FINGERLAND, HUSAK and BENDLOVA 1971 (515) 177, 165
FISHER, GORE, OKABE and WHITE 1965 (A 202) 54
FISHER 1968 (S 93) 330
FISHER, CARR, HUFF and HUBER 1970 (A 203) 54
FISHER 1958 (S 129) 332
FISHER and ZUKERMAN 1946 (A 153) 50
FITZGERALD 1969 (S 56) 327
FLASER 1964 (S 195) 336
FLEIG 1908 (786) 242, 241
FLETCHER 1971 (S 114) 331
FLETCHER 1972 (S 172) 334, 416 (h)
FLETCHER 1972 416(j)
FLETCHER and HORN 1970 (S 58) 327
FLICK 1964 (S 73) 328
FLIPSE 1960 (A 251) 116
FODOR 1967 (A 467) 189
FODOR 1970 (A 533) 193
FODOR, GLASS and WEINER 1968 (S 95) 330
FOGELHOLM 1970 (159) 72, 71
FOLIGUET, WERNER and VERT 1963 (77) 44, 43
FOLKOW and VON EULER 1954 (A 701) 257
FOLLE, SAMANEK and AVIADO 1966 (906) 272, 270, 365 (a)
FONTANA 1960 (112) 66, 62
FONTANA, REDISCH, NEMIR, SMITH, DeCRINIS and SULZBERGER 1959 (113) 66, 62
FOOD AND COSMETICS TOXICOLOGY 1968 (S 238) 340
FORBES 1958 (S 185) 336
FORTE, WILLIAMS, POTGIETER, SCHMITT-HENNER, HAFKENSCHIEL and RIEGEL 1960 (907) 272, 270
FOWLER 1972 (A 5) 12
FOX and HASKELL 1968 (A 398) 143

100505051

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

FOX, NAUGHTON and GORMAN 1972 (A 347) 140
FOX and PAUL 1969 (A 399) 143
FOX and SKINNER 1964 (A 397) 143
FOX 1969 (S 106) 330
FRANK 1968 (228) 93, 89
FRANK 1968 (A 400) 143
FRANK, WEINBLATT and SAGER 1966 (229) 93, 89
FRANK, WEINBLATT, SHAPIRO and SAGER 1966 (405) 150, 148
FRANK, WEINBLATT, SHAPIRO, SEIDEN and SAGER 1963 (230) 93, 89
FRANKL, FRIEDMAN and SOLOFF 1966 (818) 248, 247
FRANKL, FRIEDMAN, WILSON and SOLOFF 1965 (729) 236, 230
FRANKL and SOLOFF 1967 (732) 236, 230
FRANKL, WINTERS and SOLOFF 1965a (730) 236, 232, 388 (a)
FRANKL, WINTERS and SOLOFF 1965b (731) 236, 232
FREDERIKSEN and RAVENHOLT 1970 (691) 218, 216
FREDRICKSON 1968 (S 94) 330
FREDRICKSON 1970 (S 109) 331
FRENCH and CAPLAN 1970 (A 301) 119
FREUND and WARD 1960 (787) 242, 241
FRIBERG 1972 (S 173) 334, 424 (b)
FRIBERG, CEDERLOF, LUNDMAN and OLSSON 1970 (318) 109, 108
FRIBERG, KALJ, DENCKER and JONSSON 1959 (317) 109, 107
FRICK and MIETTINEN 1971 (A 74) 29
FRIEDELL 1953 (788) 242, 241
FRIEDMAN and HELLERSTEIN 1968 (494) 174, 163
FRIEDMAN 1967 (280) 99, 97
FRIEDMAN 1968 (114) 66, 64
FRIEDMAN, KANNEL, DAWBER and McNAMARA 1967 (185) 85, 82
FRIEDMAN, LOVELAND and EHRLICH 1967 (A 204) 54
FRIEDMAN, BYERS, ROSENMAN and ELEVITCH 1970 (388) 136, 134
FRIEDMAN and ROSENMAN 1959 (389) 136, 134
FRIEDMAN and ROSENMAN 1971 (390) 136, 134
FRIEDMAN and ROSENMAN 1972 (A 348) 140
FRIEDMAN, ROSENMAN and BYERS 1964 (A 567) 196
FRIEDMAN, ROSENMAN and CARROLL 1958 (A 566) 196
FRIEDMAN, ROSENMAN, STRAUS, WURM and KOSITCHEK 1968 (82) 58
FRIEDMAN, ST. GEORGE, BYERS and ROSENMAN 1960 (391) 136, 134
FRIEDMAN, ST. GEORGE, BYERS and ROSENMAN 1960 (A 702) 257
FROELICHER and OBERMAN 1972 (A 401) 143
FROMMEL 1928 (871) 265
FULMER and ROBERTS 1963 (231) 93, 90
FURBINGER 1926 (14) 19, 15
FURBINGER 1923 (S 12) 324
FURBINGER 1926 (S 13) 324
FUREY, SCHAANNING, SPOONT and BIRKENHEAD 1967 (789) 242, 241
FURMAN 1968 (358) 128, 126
FURST, GREAVES, HAWTHORNE, McCARTNEY and STEWART 1972 (S 174) 334
GAEDE 1941 (A 731) 260
GAENSLER, CADIGAN, ELLICOTT, JONES and MARKS 1957 (996) 293, 29
GALLAVARDIN 1924 (A 633) 225
GARCIA-PALMIERI, COSTAS, CRUZ-VIDAL CORTES-ALICEA, COLON, FELIBER AYALA, PATTERNE, SOBRINO, TORRES and NAZARIO 1970 (595) 183, 169
GARLAND 1962 (S 133) 332
GARRETT, FARHI and MANN 1967 (A 402) 143
GARRISON, McDONOUGH, HAMES and STULES 1966 (232) 93, 89
GATGOUNIS and AYCOCK 1963 (A 703) 257
GATGOUNIS, RICHARDSON and CLAYTON 1964 (A 704) 258
GAU, GOODWIN, OAKLEY, OLSEN, RAHIM TOOLA, RAPHAEL and STEINER 1972 (A 538) 194
GAZES, RICHARDSON and WOODS 1959 (A 732) 260
GEBBER and VOLLE 1966 (A 676) 255
GELIN, ELGRISHI, DUCIMETIERE and RICHARD 1967 (635) 205
GELINEAU 1862 (15) 19, 15
GENERAL PRACTITIONER 1967 (A 101) 31
GERTLER, WELSH and WHITER 1966 (A 20 54
GERTLER, WHITER and WELSH 1967 (A 25 116
GERTLER, WOODBURY, GOTTSCH, WHITE and RUSK 1959 (376) 133, 131
GERTLER, LEETMA, RUSK, COVALT, SALUSTE and ROSENBERGER 1969 (A 205) 54
GERTLER, DRISKELL, BLAND, GARN, LERMAN, LEVINE, SPRAGUE and WHITE 1951 (340) 124, 123, 122
GETTLER and MATTICE 1933 (997) 293, 29
GIAMPAGLIA, MARCHESE and LEONE 1972 (115) 66, 65

10050852

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GIBELLI, BOLANDRINA, DEL FAVERO and PASOTTI 1964 (692) 218, 215
GIBBONS and MITROPOULOS 1972 (1099) 312, 310
GILBERT 1936 (A 634) 225
GILDER 1971 (S 164) 334
GILFILLIAN 1912 (16) 19, 15
GILLMANN and COLBERG 1969 (A 487) 190
GINZEL and KOTTEGA 1954 (A 677) 256
GIOVANELLI 1964 (S 41) 326
GITTELSOHN and KINCH 1965 (A 220) 77
GLASS, GARRETA, LEWIS, GRAMMATICOS and SZUR 1968 (1148) 319, 316
GLAZUNOV, ARONOV, DROMBIAN and DRYLOVA 1964 (611) 185, 170
GLORIOSO 1967 (A 42) 27
GLYNN, MUSTARD, BUCHANAN and MURPHY 1966 (858) 252, 250
GODBER 1970 (S 59) 327
GOFMAN, LINDGREN, STRISOWER, DELALLA, GLAZIER and TAMPLIN 1955 (658) 211, 209
GOKSEL 1967 (819) 248, 246
GOLDBARG, MORAN, CHILDERS and RICKETTS 1970 (406) 150, 149
GOLDBERG, KRONE, and RESNEKOV 1971 (790) 242, 240
GOLDRICK, SINNETT and WHYTE 1969 (A 455) 188
GOLDSCHLAGER, CORSINI, BOETTCHER, LEB, DERNTL and BING 1969 (A 27) 14
GOLDSMITH 1970 (1062) 306, 300
GOLDSMITH and LANDAW 1968 (1149) 319, 315
GOLDSMITH, SCHUETTE and NOVICK 1963 (998) 293, 288
GOLDSMITH, TERZAGHI and HACKNEY 1963 (1028) 298, 297
GOLDSTEIN and BECK 1965 (A 751) 262
GOLDSTEIN and EPSTIEN 1972 (A 6) 12
GOLDSTEIN 1937 (17) 19, 15
GOLUBOVSKI 1968 (609) 185, 169
GOODMAN, ELIAN, MOZES and DEUTSCH 1965 (116) 66, 61
GOOSSENS and MESSIN 1966 (501) 176, 164
GORDON and KANNEL 1971 (186) 85, 83
GORDON and KANNEL 1972 (160) 72, 71
GORDON and KANNEL 1972 (A 221) 77
GORLIN, BRACHFELD, MacLEOD and BOPP 1959 (A 75) 29
GOTHERT, LUTZ and MALORNY 1970 (1100) 312, 308
GOTTHEINER 1971 (A 76) 29
GOULET, ALLARD and POIRIER 1968 (510) 177, 164
GABRIEL, STARR and WHITE 1938 (733) 236, 228)
GRAHAM, COVELL, SONNENBLICK, ROSS and BRAUNWALD 1968 (A 733) 260
GRANNIS 1971 (S 165) 334, 470 (a)
GRANT 1968 (S 152) 333
GRAY, BOOKER and OXHOA 1967 (A 705) 258
GREEN and HORN 1968 (S 96) 330
GREEN 1942 (117) 66
GREEN and BOROUSCH 1960 (A 102) 31
GREEN and GEISS 1961 (A 154) 50
GREENBERG 1972 (A 497) 191
GREENBERG and WHEREAT 1970 (S 212) 337
GREENHALGH, LEWIS, ROSENGARTEN, CALNAN, MERVART and MARTIN 1971 (118) 66, 61
GREENSPAN, EDMANDS, KNOEBEL and FISCH 1969 (872) 265
GREWAL, LU, and ALLMARK 1960 (A 678) 256
GREWAL, LU and ALLMARK 1962 (A 706) 258
GROEN 1969 (A 155) 1969
GROOM, McKEE, WEBB, GRANT, PEAN and HUDICOURT 1959 (83) 58
GROSGOGEAT and ROUBELAKIS 1965 (947) 279, 277
GROSGOGEAT, ANGUERA, LELLOUCH, JACOTOT and BEAUMONT 1965 (959) 281, 280
GROSS 1970 (659) 211
GROSSMAN 1967 (A 7) 12
GROSSMAN and BURKO 1968 (A 284) 118
GRUT, ASTRUP, CHALLEN and GERHARDSSON 1970 (1150) 319, 315
GSELL 1966 (342) 124
GSELL and ABELIN 1972 (A 231) 102
GUDBJARNASON 1968 (960) 281, 280
GUILLERM, BADRE and GAUTIER 1967 (1063) 306, 302
GUION and MEARA 1928 (A 635) 225
GUNDERSON and HOYT 1971 (A 207) 54
GUPTA, MITTAL and MEHROTRA 1964 (660) 212, 209
GUSMAN and KHALFEN 1959 (734) 236, 231
GUTENKAUF, BRATT and ELIOT 1967 (1151) 319, 315
GUTIERREZ MOYANO 1968 (A 156) 50
GUTIERREZ MOYANO and DAYRIT 1969 (594) 183, 169
GUY, SALHANY and ELIOT 1971 (1152) 319, 317
GWEE and LEE 1970 (A 43) 27

10050853

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

HAAG 1957 (457) 160, 171
HAAG; LARSON; WEATHERBY (735) 234, 236
HAAS; ANAGNOSTU; LANG and SCHMIDT 1970 (407) 149
HADDOCK 1970 (161) 71, 72
HAFT, LAU, DAMATO 1966 (736) 233, 236
HAGERUP 1971 (623) 201
HAHN 1968 (A 302) 119
HALHUBER 1971 (A 193) 31
HALHUBER 1972 (A 104) 31
HALL 1968 (A 752) 262
HALL 1972 (281 98, 99
HALL 1968 (458 160, 171
HALPERIN; BLACKWELDER and VERTER 1971 (392), 135, 136
HALSEY 1933 (119 62, 66
HAMILL AND O'NEILL 1969 (1029 297
HAMMOND 1958 (187) 79, 85
HAMMOND 1960 (188) 79, 85
HAMMOND 1962 (S 38) 326
HAMMOND 1962 (189) 79, 86
HAMMOND 1963 (190) 79, 86
HAMMOND 1964 (191) 78, 86
HAMMOND 1966 (162 70, 72
HAMMOND 1967 (S198) 337
HAMMOND 1968a (192) 79, 86
HAMMOND, AUERBACH, KIRMAN and GARFINKEL 1970 (738) 233, 236
HAMMOND and GARFINKEL 1966 (194) 79, 86
HAMMOND and GARFINKEL 1968b (193) 79, 86
HAMMOND AND GARFINKEL 1969 (195) 79, 86
HAMMOND, GARFINKEL and SEIDMAN 1971 (377) 130, 133
HAMMOND and HORN 1954 (196) 78, 86
HAMMOND and HORN 1958a (197) 78, 86
HAMMOND and HORN 1958a (198) 78, 86
HAMNER, MEHTA, PINDBORG, ODONT and DAFTARY 1971 (A 512) 192
HAMPTON and MITCHELL 1966 (978) 282, 284
HANSEN 1968 (A 285) 118
HANSON and HASTING 1933 (1030) 297, 298
HANSON 1962 (737) 229, 236
HANSSON, MASUOKA and CLARK 1963 (A 707) 258
HANSSON, MASUOKA and CLARK 1964 (A 708) 258
HARKAVY 1933 (120) 62, 66
HARKAVY 1956 (123) 62 66
HARKAVY 1957 (122) 62, 66
HARKAVY 1968 (121) 62, 66
HARKAVY 1970 (124) 62, 66
HARKAVY 1932 (124a) 62, 66
HARKAVY 1960 (125) 62, 66
HARKAVY 1962 (126) 62, 66
HARKAVY and PERLMAN 1964 (127) 62, 66
HARKEN 1968 (S 97) 330
HARLAN, OBERMAN, MITCHELL and GRAYBIEL 1967 (820) 248, 247
HARLAND 1971 (A 125) 47
HARRIS 1939 (S 64) 328
HARRISON and MITCHELL 1966 (A 605) 199
HARTRIDE 1919-1920 (1000) 293, 290, 287
HARTROFT 1956 (359) 128, 126
HASHIMOTO; IGARASHI, UE! and KUMAKURA 1964 (879) 268, 265
HASLAM 1964 (A 606) 199
HASS, HENSON; LANDERHOL and HEMMENS 1968 (950) 279 277
HASS, LANDERHOLM and HEMMENS 1966a (948) 279, 277
HASS; LANDERHOLM and HEMMENS 1966b (949) 279, 277
HASSENCAMP 1939 (A 734) 260
HATCH, REISSELL, POON-KING, CANELLOS, LEES and HAGOPIAN 1966 (343) 124, 123, 122
HAUGE, HARVALD and REID 1970 (319) 109, 108
HAVARD 1966 (A 44) 27
HAVLIK, FEINLEIB, GARRISON and KANNEL 1969 (707) 221, 220
HAWKINS 1972 (693) 218 215
HAY 1972 (S 62) 327
HAY and TURBOTT 1970 (69) 42, 40
HAYWOOD, WALBERG, KERR, MOSHSENIN, and MOHLER 1972 (1064) 306, 300
HEAD 1939 (S 17) 324
HEBERDEN 1802 (18) 19, 15
HECHT 1962 (S 134) 332
HEDBERG and LINDBERG 1969 (A 534) 193
HEDRICK 1971 (S 115) 331
HEFFERNAN, CULLEN; O'SULLIVAN, BUGLER and MULCAHY 1968 (A 77) 29
HEGGLIN and KEISER 1955 (S 25) 325
HEINE , SCHMIDT and ANDERS 1965 (A 181) 52
HEISTAD and WHEELER 1972 (1101) 308, 312
HELLBERG, WAYLAND, RICKART and BING 19 (908) 272, 270
HELLERSTEIN 1968 (A404) 143

100505054

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

HELLERSTEIN 1968 (A 404) 143
HELLERSTEIN and FORD 1968 (A 78) 30
HELLUNG-LARSEN, LAURSEN, KJELDSEN, ASTRUP 1968 (1102) 312, 309
HENDERSON 1953 (739) 228, 236
HERBIG 1942 (A 679) 256
HERMAN, ELLIOTT and GORLIN 1967 (A 539) 194
HERNBERG 1964 (661) 212, 209
HERRMANN 1929 (A 636) 225
HERSHBERG 1968 (A 79) 30
HERSHBERG and ALEXANDER 1972 (A 80) 30
HETZEL 1972 (A 350) 140
HEYDEN and GERBER 1969 (A 208) 54
HEYDEN, CASSEL, BARTELL; TYROLER, HAMES 1971 (415) 152, 151
HEYDEN, HAMES, BARTEL, CASSEL, TYROLER 1971 (416) 152, 151
HEYDEN-STUCKY 1965 (662) 212, 210
HEYDEN-STUCKY 1967 (608) 185, 169
HICKEY, GEARTY, BOURKE and MULCAHY (A 499) 191
HICKEY and MULCAHY 1970 (A 498) 191
HICKIE 1968 (A 351) 140
HIGGINS 1964 (A 182) 52
HIGGINS, HIGGINS; LOCKSHIN and CANALE 1969 (496) 176, 163
HIGGINS, LOCKSHIN, GILSON, COCHRANE, CAMPBELL, WATERS; FERRIS, OH, HIGGINS 1972 (326) 113, 112
HIGGINS and KELLER 1970 (233) 93, 90
HIGGINS and KJELSBERG 1967 (234) 93, 90
HILLEBOE 1957 (282) 99, 98
HIMBERT, BENSAID and ROUSSEL 1971 (530) 178, 165
HINES 1960 (791) 242, 241
HINKLE 1966 (487) 174, 163
HINKLE 1967 (A 253) 116
HINKLE 1971 (A 45) 27
HINKLE 1972 (489) 174, 163
HINKLE 1966 (S 86) 329
HINKLE 1968 (488) 174, 163
HIPSLEY 1971 (S 166) 334
HIPSLEY 1971 (S 116) 331
HIPSLEY 1966 (A 456) 188
HIRAYAMA 1972 (A 521) 192
HISLOP 1964 (S 197) 336
HJERMANN 1971 (A 527) 193
HLOUCAL and DUSEK 1968 (512)
HLOUCAL and DUSEK 1969 (A 468) 189
HLOUCAL and DUSEK 1971 (A 352) 140
HLOUCAL and DUSEK 1971 (A 143) 49
HOAK, CONNOR, ECKSTEIN and WARNER 1964 (A 607) 199
HOAK, POOLE and ROBINSON 1963 (A 608) 199
HOAK, WARNER and CONNOR 1967 (A 609) 199
HOFF and HOCKMAN 1967 (A 753) 262
HOFFMANN 1914 (A 183) 52
HOFREUTER, CATCOTT and XINTARAS 1962 (1001) 293, 291
HOLCZABEK 1971 (1065) 306, 303
HOLLANDS and VANOV 1965 (A 709) 258
HOLLAND, RAFTERY, McPHERSON and STONE 1967 (479) 173, 162
HOLMGREN 1967 (A 405) 143
HONEGGER 1967 (A 105) 31
HOOD, TIBBLIN, WELIN, ORNDAHL and KORSAN-BENGTSEN 1969 (A 286) 118
HORAK, KOCI and PLISEK 1968 (513) 177, 165
HORLEIN and SEITZ 1968 (A 488) 190
HORVATH 1969 (A353) 140
HOSPITAL MEDICINE 1968 (S 280) 343
HOWARD 1934 (A 157) 50
HOWE 1970 (A 500) 191
HOWELL 1971 455(a)
HOWELL 1972 (S 175) 335
HOWELL 1972 (S 176) 335
HRACHOVEC 1969 (A354) 140
HSI-PU S and LI-MING 1940 (1031) 298, 297
HUCHARD 1899 (19) 19, 16
HUEPER 1941 (A 126) 47
HUEPER 1943 (951) 279, 277
HUEPER 1944 (1103) 312, 309
HUGHES 1962 (S 135) 332
HUGHES 1970 (663) 212, 207
HULTGREN, CALCIANO, PLATT and ABRAMS 1967 (84) 58, 55
HUNT 1956 (A 637) 225
HUNTER 1961 (A 568) 196
HUNTER 1962 (A 569) 197
HUNTER 1963 (589) 183, 168
HURST and SCHLANT 1960 (A 158) 50
HUTCHISON 1968 (S 317) 346
HUTCHISON 1970 (428) 155, 153
HYAMS and LOOP 1969 (486) 174, 163
HYAMS, SEGI and ARCHER 1967 (53) 35, 34
IGLESIAS, CARIS and LANCASTER 1971 (626) 203, 201
IKKALA 1960 (516) 177, 165
INGALLS and GORDON 1966 (A 355) 140
INTERNATIONAL SYMPOSIUM IN SAN JUAN 1971 (320) 109, 108
IRVING and YAMAMOTO 1963 (740) 236, 230
ISACSSON 1972 (128) 66, 61

1005050855

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JACKSON, OBERMAN, MITCHELL and GRAYBIEL 1967 (741) 237, 228
JACKSON 1891 (A 638) 225
JACOBS 1971 (600) 184, 169
JACOBS 1968 (85) 58
JAFFE 1968 (1066) 300
JAKUSZEWSKA 1969 (344) 124,123
JAMES (742) 237
JAMES 1968 (S 51) 327
JAMES, POST, SMITH 1955 (361) 128, 127, 126
JAN and GROSGOGEAT 1971 (S 60) 327
JAN, LACOTOT and BEAUMONT 1969 (977) 284, 282
JENKINS 1967 (A 303) 119
JENKINS 1971 (A 304) 119
JENKINS, ROSEMAN and ZYZANSKI 1968a (235) 93, 90
JENKINS, ROSEMAN and ZYZANSKI 1968b (236) 93, 90
JENKINS, ROSEMAN and ZYZANSKI 1968 (664) 212, 207
JHATAKIA 1966 (557) 180, 167
JHATAKIA; THAKORE and VASAVADA 1967 (559) 180, 167
JICK, SLONE, WESTERHOLM, INMAN, VESSEY, SHAPIRO, LEWIS and WORCESTER 1969 (708) 221, 220
JOHANSSON 1972 (606) 184, 169
JOHANSSON and TORP (A 8) 12
JUHASZ-NAGY, SZENTIVÁNYI, RÁCZ and DEÁK 1965 (909) 272, 271
JOHNSON and EPSTEIN 1966 (129) 66, 60
JOHNSON, YANO and KATO 1958-1964 (584) 182, 168
JOHNSON 1929 (S 14) 324
JOLLIFFE 1959 (A 570) 197
JONES, STRICKLAND, STUNKARD, SIEGEL 1971 (1153) 319, 316
JONES, RILEY, REEVES and SHEFFIELD 1972 (A 159) 50
JONGBLOED 1939 (1032) 298, 295
JORES 1964 (S 318) 346
JOULES 1956 (S 28) 325
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1963 (S 266) 342
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1963 (S 222) 339
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (S 228) 339
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1966 (S 236) 340
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1969 (S 284) 343
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1969 (S 285) 343
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1970 (S 290) 343
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1971 (S 258) 341
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1971 (S 258) 341
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1971 (S 259) 341
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1972 (S 293) 343
JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 1972 (S 292) 343
JOURNAL OF THE MEDICAL ASSOCIATION OF AMERICA (S 273) 342
JOURNAL OF THE MEDICAL ASSOCIATION OF AMERICA (S 272) 342
JOURNAL OF THE MEDICAL ASSOCIATION OF GEORGIA (S 239) 340
JOUVE, AUBERT and AVRIL 1966 (A 184) 52
JOUVE, BENYAMINE and MALATERRE 1966 (362) 128, 127
JOUVE, MALFROY and CALVIN 1963 (A 254) 116
JOUVE, ROCHU and AVRIL 1969 (130) 66, 63
JOUVE, SOMMER and AVIERINOS 1972 (A 482) 190
JUERGENS, BARKER and HINES 1960 (131) 66, 60, 65
KAGAN, DAWBER, KANNEL and REVOTSKI 1962 (199) 86, 81
KAGAN, KANNEL, DAWBER and REVOTSKI 1963 (200) 86, 82
KAGAN, RHOADS, ZEEGEN and NICHAMAN (474) 172, 162
KAHLSON 1937 (A 540) 194
KAHN 1966 (163) 70, 72
KAHN, MEDALIE, NEUFELD; RISS and GOLDBOURT 1972 (636) 205, 204
KAKO, CHRYSOHOU 1960 (A 735) 260
KAKO, CHRYSOHOU 1961 (A 736) 261
KAKOWSKI 1906 (S 9) 323
KALTENBACH, SCHÄFER and KLEPZIG 1967 (A 541) 194
KALTENBACH, SCHÄFER and KLEPZIG 1967 (743) 237, 228
KANDASWAMY 1970 (A 513) 192
KANNEL 1964 (S 74) 328
KANNEL 1970 (201) 86, 83
KANNEL 1971 (164) 72, 70
KANNEL and CASTELLI 1972 (202) 86, 83
KANNEL and DAWBER 1972 (A 127) 47
KANNEL and GORDON 1971a (203) 86, 84
KANNEL AND GORDON 1971b (204) 84, 86
KANNEL and McNAMARA 1964 (205) 83, 86
KANNEL, CASTELLI and McNAMARA 1967 (206) 86, 82
KANNEL, DAWBER and McNAMARA 1966 (207) 87, 82
KANNEL, GORDON and SCHWARTZ 1971 (638) 205, 204
KANNEL, SCHWARTZ and McNAMARA 1969 (208) 87, 83
KANNEL, WIDMER and DAWBER 1965 (209) 87, 82

10050856

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KANNEL, CASTELLI, GORDON and McNAMARA 1971 (665) 212, 207
KANNEL, CASTELLI, MCNAMARA and SORLIE 1969 (637) 205, 204
KANNEL, DAWBER, COHEN and McNAMARA 1965 (165) 72, 70
KANNEL, GORDON, WOLF and McNAMARA 1972 (166) 72, 70
KANNEL, KAGAN, DAWBER and REVOTSKIE 1962b (210) 87, 81
KANNEL, DAWBER, SKINNER, McNAMARA and SHURTLEFF 1965 (132) 66, 60
KAPLAN 1967 (A 287) 118
KAPLAN, JACQUES and GANT 1957 (961) 281, 280
KAPLAN, CASSEL, TYROLER; CORNONI, KLEINBAUM and HAMES 1971 (468) 172, 162
KAPPERT 1971 (429) 155, 153, 484 (a)
KAREVA 1963 (910) 272, 271
KARVONEN 1962 (520) 178, 165
KARVONEN 1971 (522) 178, 165
KARVONEN 1972 (523) 178, 165
KARVONEN, RAUTAHARJU, ORMA, PUNSAR, TAKKUNEN 1961 (517) 177, 165
KARVONEN, ORMA, PUNSAR, KALLIO, ARSTILA, LUOMANMAKI and TAKKUNEN 1970 (521) 178, 165
KARVONEN, BLOMQVIST, KALLIO, ORMA, PUNSAR, PAUTAJARJU, TAKKUNEN and KEYS 1967 (519) 178, 165
KASANEN and FORSSTRÖM 1966 (54) 35,33
KASANEN and FORSSTRÖM 1966 (446) 159, 158
KASANEN, KALLIO and FORSSTRÖM 1963 (A 305) 119
KASPARIAN 1964 (S 319) 346
KASSIR 1968 (A 571) 197
KASTL 1969 (A 489) 190
KATTUS, JORGENSEN, WORDEN and LAVARO 1971 (624) 203, 202
KATZ 1960 (A 160) 50
KATZ 1972 (A 144) 49
KATZ and PICK 1962 (A 145) 49
KATZCHMANN 1970 (1067) 306, 302
KAUFMANN and BENSIMON 1960 (A 710) 258
KAUFMANN, BENSIMON and BERGOGNE 1959 (792) 242, 240
KAYMAKCALAN, TÜRKER, KIRAN and KAYAN 1968 (744) 237, 233
KEDRA and DMOWSKI 1966 (133) 68, 60
KEDRA and KOROLKO 1965 (853) 251, 250
KEDRA and KOROLKO 1966 (694) 218, 214
KEDRA, POLESZAK, PITERA 1965 (821) 248, 247
KEIDITSCH and LANGER 1967 (A 161) 50
KEISER 1954 (532) 179, 165
KELLER 1922 (20) 20, 18, 15
KELLER 1970 (A 429) 146
KELLER, ANTHONY and GRESHAM 1970 (A 429) 146
KEMP 1971 (S 117) 331
KERR, PIRRIE, MacAULAY and BRONTE-STEWARD 1965 (A 610) 199
KERRIGAN, JAIN and DOYLE 1968 (793) 242, 24
KERSHBAUM 1967 (823) 248, 246
KERSHBAUM 1968 (822) 248, 247
KERSHBAUM and BELLET 1964 (824) 248, 246
KERSHBAUM and BELLET 1966 (825) 248, 246
KERSHBAUM and BELLET 1968 (826) 248, 247
KERSHBAUM, BELLET and KHORSANDIAN 1965 (962) 281, 280
KERSHBAUM, JIMENIZ and BELLET 1964 (832) 249, 246
KERSHBAUM, BELLET, CAPLAN and FEINBERG 1962 (827) 248, 246
KERSHBAUM, BELLET, CHO and DUGGE 1965 (828) 248, 247
KERSHBAUM, BELLET, DICKSTEIN and FEINBERG 1960 (829) 249, 246
KERSHBAUM, BELLET; DICKSTEIN and FEINBERG 1961 (830) 249, 246
KERSHBAUM, BELLET, HIRABAYASHI and FEINBERG 1967a (963) 281, 280
KERSHBAUM, BELLET, JIMENEZ and FEINBERG 1966 (831) 249, 247
KERSHBAUM, JIMINEZ; BELLET and ZANUTTINI 1966 (965) 281, 280
KERSHBAUM, PAPPAJOHN, OSADA and BELLET 1967b (835) 249, 247
KERSHBAUM; BELLET, HIRABAYASHI, FEINBERG and EILBERG 1967 (875) 265, 264
KERSHBAUM, KHORSANDIAN, CAPLAN, BELLET and FEINBERG 1963 (833) 249, 246
KERSHBAUM; OSADA, SCIABINE, BELLET and PAPPAJOHN 1967b (964) 281, 280
KERSHBAUM, PAPPAJOHN, BELLET, HIRABAYASHI 1967a (834) 247, 249
KERSHBAUM, PAPPAJOHN, BELLET, HIRABAYASHI and SHAFIHA 1968 (836) 249, 247
KEYES, MIZUKAMI AND LUMRY 1967 (1154) 319, 315
KEYS 1957 (A 430) 246
KEYS 1962 (447) 159, 157
KEYS 1967 (A 255) 116
KEYS 1968 (A 573) 197
KEYS 1969 (A 356) 140
KEYS 1970 (327) 113, 112
KEYS 1971 (430) 155, 154
KEYS 1972 (A 222) 77
KEYS and BLACKBURN 1963 (A 256) 116
KEYS, BLACKBURN and TAYLOR (A 223) 77
KEYS, TAYLOR, SIMONSON, BLACKBURN and ANDERSON 1961 (A 572) 197
KEYS, TAYLOR, BLACKBURN, BROZEK, ANDERSON and SIMONSON 1971 (237) 93, 90

10050857

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KEYS; ARAVANIS; BLACKBURN, VAN BUCHEM, BUZINA, DJORDJEVIC, FIDANZA, KARVONEN, MENOTTI, PUDDU and TAYLOR 1972 (417) 152, 151
KEYS; ARAVANIS; BLACKBURN; VAN BUCHEM, BUZINA, DJORDJEVIC, FIDANZA; KARVONEN; MENOTTI, PUDDU and TAYLOR 1972 (238) 93, 90
KHOSLA and LOWE 1971 (418) 152, 151
KIDNER 1969 (A 81) 30
KIEF 1970 (A 574) 197
KIEN and SHERROD 1960 (746) 237, 233
KIEN, LASKER and SHERROD 1957 (911) 22, 270
KIEN; LASKER and SHERROD 1958 (745) 237, 233
KIMURA 1967 (583) 182, 168
KIMURA, TOSHIMA; NAKAYAMA, MIZUGUCHI, TAKAYMA, FUKAMI, TASHIRO, KATAYAMA, ABE, ARIMA, YOKOTA, MINAGAWA, TANAKA, AKIYOSHI, SOEJIMA, YAMADA; MIZUNOE, NAKAMURA, OSHIMA, TANAKA, AKASU, NIIZAKI, IKEDA, NAKAMICHI, AGETA, MIIKE; INOU; NAKAGAWA, NANBU, TANIOKA; SHIMADA and FUKUMOTO 1972 (167) 72, 70
KING 1970 (301) 106, 105
KIRKEBY 1966 (A 575) 197
KIRSHNER, SAGE, SMITH and KIRSHNER 1966 (A 711) 258
KISTLER 1965 (S 80) 329
KJELDSEN 1969 (1104) 312, 309
KJELDSEN 1970 (1105) 312, 309
KJELDSEN 1970 (1106) 312, 309
KJELDSEN and DAMGAARD 1968 (1109) 312, 309
KJELDSEN and DAMGAARD 1968 (1155) 319, 316
KJELDSEN and MOZES 1969 (134) 68, 63
KJELDSEN and MOZES 1969 (1110) 312, 309
KJELDSEN, ASTRUP and WANSTRUP 1969 (1107) 312, 309
KJELDSEN, ASTRUP and WANSTRUP 1972 (1108) 312, 309
KJELDSEN, WANSTRUP and ASTRUP 1968 (1111) 312, 309
KJELSBERG and STAMLER 1960 (239) 93, 90
KLAUSEN, RASMUSSEN; GJELLEROD, MADSEN and PETERSON 1968 (1068) 306, 302
KLEE 1962 (A 9) 12
KLEIN 1966 (A 128) 47
KLEINBAUM, KUPPER, CASSEL and RYROLER 1971 (240) 93, 89
KLENSCH 1963 (747) 237, 229
KLENSCH 1966 (873) 265, 264
KLENSCH; SPECKMANN; MAETZEL and MEYER 1967 (874) 265, 264
KLINK 1970 (360) 128, 126
KLUGMAN, MAGRIS, MIAN and FANNA (A 46) 27
KNAPPE, STRUBE, DÜCK, RELKE and RITTMEISTER 1970 (A 490) 190
KOHN 1926 (21) 20, 15
KOHN 1926 (A 639) 225
KOLLER 1968 (S 52) 327
KOMCZYNSKI 1958 (748) 237, 234
KONTTINEN 1962 (666) 212, 209
KONTTINEN 1963 (837) 249, 247
KORNITZER; DEMEESTER and DENOLIN 1971 (A 461) 188
KORNITZER, DEMEESTER; DELCOURT, GOOSSENS and BERNARD 1971 (667) 212, 209
KORNITZER, DEMEESTER, DELCOURT and BERNARD 1971 (A 462) 188
KORSAN-BENGSTEN 1970 (A 611) 200
KORSAN-BENGSTEN 1972 (695) 218, 215
KOSHY 1962 (S 188) 336
KOSTER 1970 (A 357) 140
KOZAREVIC, PIRC, DAWBER, KAHN and ZUKEL 1971 (612) 185
KRADJIAN, BOWLES and EDWARDS 1971 (A 185) 52
KREHL and HODGES 1965 (A 162) 50
KREYBERG, DABLE; POPPE; EFSKIND, PEDERSEN; ELDJARN, and DEVIK 1967 (S 47) 326
KRITSKIKIS, WARNKE and PARSI 1967 (A 257) 116
KRONE, GOLDBARG, BALKOURA, SCHUESSLE and RESNEKOV 1972 (794) 240, 242
KROSNICK 1967 (431) 155, 153
KRUEGER, WILLIAMS and PAFFENBARGER 1967 (A 209) 54
KRÜGER 1972 (A 358) 140
KRUMHOLZ, CHEVALIER and ROSS 1964 (749) 237, 232, 362 (a)
KRUMHOLZ, CHEVALIER and ROSS 1964 (1069) 306, 302, 367 (a)
KRUMHOLZ; CHEVALIER and ROSS 1965 (1070) 306, 302
KRUT 1968 (A 129) 47
KRUT, PERRIN and BRONTE-STEWART 1961 (448) 159, 157
KRYSA 1966 (22) 20, 16
KUHN 1967 (795) 243, 241
KUKOVETZ 1961 (A 680) 256
KULLER and LILIENFELD 1966 387(a)
KULLER, LILENFELD and FISHER 1966 (A 47) 27
KULLER, LILIENFELD and FISHER 1966 (A 288) 118
KUMLIN 1959 (S 30) 325
KUNDU 1972 (A 359) 140
KUPKE 1972 (952) 279, 278
KURIEN and OLIVER 1966 (668) 212, 207
KURLAND and FREEDBERG 1968 (A 576) 197

10050858

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

KUTNER 1970 (A 106) 37
KUTSCHA 1968 (A 360) 140
KUTSCHERA-AICHBERGEN 1943 (S 19) 324
LACY 1968 (S 153) 333
LAESSING 1938 (A 681) 256
LAFRENZ 1967 (A 10) 12
LAFRENZ 1970 (625) 3, 201
LAL and CAROLI 1967 (560) 180, 167
LAL and CAROLI 1968 (561) 181, 167
LAMBER 1935 (A 11) 12
LAMPSON 1935 (796) 243, 240
LANCET 1964 (S 230) 339
LANCET 1964 (S 229) 339
LANCET 1969 (S 246) 340
LANCET 1969 (S 247) 340
LANCET 1970 (S 251) 340
LANCET 1971 (S 260) 341
LANDERHOLM, HEMMENS and HASS 1967 (953) 209, 277
LARSON 1960 (877) 268, 264
LARSON, FUKUDA and MURRAY 1965 (912) 273, 271
LARSON, HAIG and SILVETTE 1961 349(a)
LARSON, MURRAY 1963 (878) 268, 266
LASLETTER 1921 (A 640) 225
LAUBRY; WALSER and DEGLAUDE 1933 (913) 270, 273
LAUDA 1961 (A 737) 261
LEADERS and LONG 1962 (914) 273, 270
LEADERS and LONG 1962 (A 682) 256
LEADERS and LONG 1962 (A 683) 256
LEAMAN 1964 (S 75) 329
LEB, DERNTL, ROBIN and BING 1970 (915) 273, 270, 429 (a)
LEE and SCHNEIDER 1958 (483) 173, 163
LEE 1908 (797) 243, 240
LELLOUCH and BEAUMONG 1967 (669) 212, 209
LELLOCH, JACOTOT, ANGUERA, GROSGOGEAT and BEAUMONT 1968 (954) 279, 277
LEMON and KUZMA 1969 (283) 99, 98
LEMON and WALDEN 1966 (241) 93, 91
LENEGRE 1967 (A 130) 47
LENZNER and ARONSON 1972 (A 306) 119
LEODOLTER, HEIL and FRANK 1971 (A 612) 200
LEREN 1966 (449) 159, 157
LEREN 1967 (A 131) 47
LEREN 1970 (A 528) 193, 464 (a)
LEUBHTENBERGER; LEUCHTENBERGER and WEISS
LEVENE 1972 (A107) 31
LEVY and GLUECK 1969 (A 577) 197
LEVY 1952 (A 641) 225
LEVY 1962 (A 642) 226
LEVY, KNIGHT, MYERSON and ROSEN 1953 (S 127) 332
LEWY, MATHERS, MUELLER and
LIEBEGOTT 1965 (378) 133, 130
LIKOFF 1968 (A 82) 30
LIKOFF, KASPARIAN and LEHMAN 1964 (43) 25, 23
LIKOFF, SEGAL and KASPARIAN 1967 (1156) 319, 317
LIKOFF, SEGAL and KASPARIAN 1967 (86) 58, 55
LILIENFELD 1959 (393) 136, 134
LILIENFELD 1965 (A 224) 77
LILIENTHAL 1950 (1157) 320, 315
LILJEFORS 1970 (323) 109, 108
LILJEFORS 1970 (A 108) 31
LILJEFORS and RAHE 1970 (322) 109, 108
LINDMAR 1962 (A 684) 256
LISIEWICZ 1963 (854) 251, 250
LISTER 1971 (S 214) 337
LISZEWSKA and MICHALSKI 1970 (S 110) 331
LITTLE 1971 (S 215) 338
LITTLE, STEWART, NIESCHE and WILLIAMS 1970 (A 186) 52
LLOYD and WOLFF 1969 (A 146) 49
LOGUE 1960 (A 12) 12
LOGUE and ROBINSON 1972 (A 13) 12
LONCIN, GURIAN and LONCIN 1968 (696) 218, 215
LONGHIN, POPESCU and TRIFU 1960 (135) 68, 6
LORD 1965 (136) 68, 65
LOWE 1960 (539) 179, 166
LOWENSTEIN 1961 (639) 205, 204
LUCCHESI, SCHUSTER and EMLEY 1967 (A 754) 262
LUCMA, HELMINEN, RYTÖMAA, MEURMAN and RANTA 1972 (A 476) 189
LUEBS, COHEN, ZALESKI and BING 1966 (A 28) 14
LUKE 1962 (S 136) 332
LUKL 1969 (A 613) 200
LUKL 1971 (A 469) 189
LUKL and WEINBERG 1963 (345) 124, 123
LUMINET 1969 (A 307) 119
LUNDMAN 1966 (321) 109, 107
LUNDMAN 1970 (A 109) 31
LUNDMAN, LILJEFORS, CEDERLÖF and FRIBERG 1971 (324) 110, 108
LUPU, POPESCU and ENESCU 1961 (S 35) 326
LUPU and VELICAN 1961 (751) 237, 234
LUPU and VELICAN 1962 (752) 237, 234
MACDONALD 1963 (S 192) 336
MACFARLAND, ROUGHTON, HALPERIN and NIVEN 1944 (1034) 298, 297
MACGREGOR 1963 (A 147) 49
MACGREGOR, PETRIE and WOOD 1971 (A 14) 12
MACK, NOLTING, HOGANCAMP and BING 1959 (A 29) 14
MAGNUSON 1968 (S 154) 333
MAHADEVAN, SINGH and LUNDBERG 1966 (A 614) 200
MAINE 1902 (23) 20, 18
MAJEKODUNMI 1964 (S 320) 346
MALESANI 1967 (573) 181, 168
MALHOTRA 1967 (A 433) 146

100505059

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MALHOTRA 1967 (558) 180, 167
MALHOTRA 1968 (697) 218, 215
MALHOTRA 1971 (A 433) 1456
MANN, GARRETT, FARHI, MURRAY and BILLINGS 1969 (A 406) 144
MANOHARAN and REDDY 1968 (A 187) 52
MANTELLI and MASSONE 1968 (A 547) 195
MARCUS 1968 (A 83) 30
MARIS 1944 (S 20) 324
MARKIEWICZ 1966 (753) 237, 230
MARKS 1967 (459) 171, 160
MARKUSH and SCHAAF 1966 (285) 99, 96
MARSHALL, STANLEY and KEZDI 1969 (798) 243, 240
MARSHALL, TALBOTT and KEZDI 1966 (799) 243, 240
MARTÍNEZ RÍOS, CATRIP, SÁNZ, GUTIÉRREZ, MEDRANO, TESTELLI and SONI 1972 (37 (58, 55
MARTZ, YOUKILLIS, HARRIS, FORNEY and NICOLL 1970 (936) 276, 275
MARYLAND and BERSAY 1972 (1071) 306, 300
MARZOT, CENNI, VISCOMI and POLI 1968 (A 518) 192
MASSIE 1964 (A 361) 140
MASTER 1935 (A 542) 194
MASTER 1935 (A 163) 50
MASTER and KUHN 1967 (A 362) 140
MASTER, WEISER and RABIN 1962 (A 84) 30
MATARAZZO and SASLOW 1960 (394) 136, 134
MATHES and RIVAL 1971 (916) 273, 271, 482(a)
MATHIESEN, LARSEN and WULFF 1970 (137) 68, 62
MATHUR 1960 (556) 180, 167
MATSUBARA and SANO 1972 (800) 243, 241
MATTIOLI and MANCINI, 1959 (670) 212, 20
MATTS 1970 (A 258) 116
MAURER, HICKEY and MULCAHY 1969 (A 501) 191
MAW 1969 (A132) 47
MCARTHUR, WALDRON and DICKINSON 1958 (395) 136, 134
MCCANN, CLANCY, TRULSON and STARE 1961 (A 502) 191
MCCORMICK 1952 (55) 35, 34
MCCORMICK 1952 (A 164) 50
MCDONALD 1968 (A 615) 200
MCDONALD, LIDWELL and WRIGHT 1965 (671) 212, 209
MCDONOUGH, HAMES, GARRISON, STULB, LICHTMAN, and HEFELFINGER 1965 (243) 93, 89
MCDONOUGH, HAMES, STULB and GARRISON 1965a (242) 93, 89
MCDONOUGH, KUSUMI and BRUCE 1970 (A 188) 52
MCFARLAND, GIMBEL, DONALD and FOLKENBERG 1964 (A 645) 226
MCFARLAND 1964 (A 165) 50
MCGANDY 1969 (A 434) 146
MCILVAINE, NELSON and BARTLETT 1969 (1002) 294, 291
MCKENNIS, TURNBULL and BOWMAN 1963 (A 713) 258
MCKUSICK, HARRIS, OTTESEN, GOODMAN, SHELLEY and bloodwell 1962 (A 189) 52
MCMILLAN 1939 (A 643) 226
MCPHERSON, JUERGENS and GIFFORD 1963 (137a) 68, 65
MEADE 1968 (A 503) 191
MEADE, ARIE, BREWIS, BOND and MORRIS 1968 (138) 68, 64
MEADE, ARIE, BREWIS, BOND and MORRIS 1968 (302) 106, 104
MEADE and CHAKRABARTI (A 431) 146
MEADALIE, KAHN, GROEN, NEUFELD and RISS 1968 (569) 181, 167
MEDICAL COLLEGE OF VIRGINIA QUARTERLY 1965 (S 270) 342
MEDICAL JOURNAL OF AUSTRALIA 1964 (S 231) 339
MEDICAL JOURNAL OF AUSTRALIA 1965 (S 232) 339
MEDICAL JOURNAL OF AUSTRALIA 1968 (S 240) 340
MEDICAL JOURNAL OF AUSTRALIA 1969 (S 248) 340
MEDICAL JOURNAL OF AUSTRALIA 1970 (S256) 340
MEDICAL JOURNAL OF AUSTRALIA 1970 (S 253) 340
MEDICAL LETTER 1963 (A 644) 226
MEDICAL LETTER 1968 (A 407) 144
MEDICAL OFFICER 1968 (S 241) 340
MEDICAL RESEARCH COUNCIL 1970 (432) 155, 154
MEDICAL SCIENCE 1963 (S 267) 342
MEDICINA SOCIALE 1969 (S 286) 343
MEHEUS, EYLENBASCH, DOUMIT, VASTESAEGER and VUYLSTEEK 1972 (503) 176, 164
MEIJLER 1971 (S 118) 331
MEIGS 1948 (1003) 294, 288, 290
MEIGS 1966 (379) 133, 130
MEIGS and ALBRINK 1966 (465) 172, 162
MENOTTI 1967 (574) 182, 168
MENOTTI 1969 (A 519) 192
MENOTTI 1972 (A 232) 102
MENOTTI 1972 (582) 182, 168
MERRIMAN 1967 (408) 150, 149
MERTENS and SEGERS 1971 (A 308) 119
METCALFE, DHINDSA, EDWARDS and MOURDJINIS 1969 (709) 221, 219
MICHAELS 1966 (A 363) 141
MILLER, TRULSON, MCCANN, WHITE and STARE 1958 (A 435) 146
MILLS 1937 (363) 128, 126
MILLS 1950 (S 22) 325
MILTON 1966 (966) 281, 280
MINNHAAR 1937 (S 16) 324
MISKIC 1961 (754) 237
MISSOURI MEDICINE 1968 (S 281) 343

1005050860

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MITCHELL 1908 (24) 20, 15
MITURZYNSKA-STRYJECKA, WIDOMSKA-CZEKAJSKA and RUPNIEWSKA 1970 (838) 249, 247
MIYAZAKI 1969 (801) 243, 241
MODAN 1970 (A 259) 116
MODERN MEDICINE 1972 (S 294) 343
MODZELEWSKI and MALEC 1969 (839) 249, 247
MOERSCH 1968 (A 364) 141
MOLEIRO and MEDINA BRICENO 1968 (346) 124, 123
MOLLER and KLEIN 1970 (433) 155, 153
MONASTERIO 1960 (S 32) 325
MONSON 1970 (139) 68, 64
MONTENEGRO and STRONG 1968 (88) 58
MONTOYE 1967 (A 408) 144
MORDKOFF and COLAS 1968 (A 309) 119
MORDKOFF and PARSONS 1967 (A 310) 120
MORET 1968 (A 548) 195
MORGAN 1971 (S 167) 334
MORIYAMA 1963 (286) 99, 96
MORIYAMA, BAUM, HAENSZEL and MATTISON 1958 (287) 99, 96
MORO, MATARESE, GALLO, IARUSSI and JACONO 1972 (140) 68, 63
MORRIS 1951 (S 65) 328
MORRIS 1960 (A 233) 102
MORRIS 1961 (A 225) 77
MORRIS 1961 (A 234) 102
MORRIS 1962 (A 504) 191
MORRIS, CHAVE, ADAM, SIREY, EPSTEIN and SHEEHAN 1973 (409) 150, 148
MORRIS, HEADY, RAFFLE, ROBERTS and PARKS 1953 (A 409) 144
MORRIS, KAGAN, PATTISON, GARDNER and RAFFLE 1966 (540) 179, 166
MORRIS 1967 (478) 173, 162
MOSCHCOWITZ 1928 (26) 20, 15
MOSCHINI-ANTINORI and SOLINAS 1951 (25) 20, 17
MOSES, POWERS and SOLOFF 1964 (755) 237, 230
MOTLEY 1971 (1004) 294, 291
MOURIQUAND and BOUCHUT 1912 (A 646) 226
MOYER and MADDOCK 1940 (802) 243, 241
MUELLER 1969 (S 210) 337
MUKERJEE 1968 (347) 124, 123
MULCAHY 1966 (S 87) 329
MULCAHY 1967 (288) 100, 98
MULCAHY 1968 (A 166) 50
MULCAHY, GOFF and HICKEY 1963 (543) 179, 166
MULCAHY and HICKEY 1965 (544) 179, 166
MULCAHY and HICKEY 1965 (A 110) 31
MULCAHY and HICKEY 1966 (545) 179, 166
MULCAHY and HICKEY 1966 (546) 179, 166
MULCAHY and HICKEY 1967 (840) 249, 246, 377(a)
MULCAHY, HICKEY and MAURER 1967a (364) 128, 126, 127
MULCAHY, HICKEY and MAURER 1967b (365) 128, 126, 127
MULCAHY, HICKEY and MAURER 1969 (551) 180, 166
MULCAHY, MCGILVRAY and HICKEY 1970 (328) 113, 111
MULHAUSEN, ASTRUP and KJELDSEN 1967 (1112) 312, 309
MULINOS and SHULMAN 1940 (803) 243, 240
MUNDY and CUTTFORTH 1972 (672) 212, 209
MURCHISON and FYFE 1966 (855) 251, 250
MURPHREE, PFEIFFER and PRICE 1967 (A 755 262
MURPHY and MUSTARD 1962 (A 616) 200
MURPHY and MUSTARD 1966 (856) 251, 250
MUSCHOLL 1961 (A 738) 261
MUSHIN 1970 (S 111) 331
MUSTARD and MURPHY 1963 (857) 252, 250, 368
MUSTART 1972 (A 617) 200
NADEAU and JAMES 1967 (917) 273, 271
NAGAI 1963 (A 714) 258
NAGLE 1969 (A 48) 27
NAHUM 1962 (S 186) 336
NAHUM 1965 (S 81) 329
NAHUM 1967 (A 365) 141
NANDA 1967 (348) 124, 122
NATHAN 1949 (A 647) 226
NATVIG 1967 (A 529) 193
NATVIG, BORCHGREVINK, DEDICHEN, OWREN, SCHIOTZ and WESTLUND 1968 (A 436) 146
NAUGHTON 1967 (756) 237, 232
NAVARRO, DESOLDATI and CAMMAROTA 1964 (44) 25, 24
NEFZGER, HRUBEC and CHALMERS 1969 (710) 221, 220
NEILL 1968 (A 30) 14
NERI, MANDEL, O'CONNOR and LARSON 1970 (A 464) 188
NEU 1958 (A 648) 226
NEUMANN and PIERACH 1965 (A111) 31
NEWTON, SEALE, O'BRIEN and MCGUIRE 1970 (45) 25, 23
NEWTON, SEALE, O'BRIEN and MCGUIRE 1970 (89) 58, 55
NEW ZEALAND MEDICAL JOURNAL 1971 (S261) 341
NEW ZEALAND NATIONAL HEART FOUNDATIO 1971 (A 525) 193
NICOLAYSEN 1964 (A 437) 146
NIELSEN 1971 (1113) 313, 308
NIEVEEN, CHAPPIN, MAY, HARTMAN, VAN DE WALL and WOUDA 1971 (A 290) 11
NIEVEEN, DOORENBOS, CHAPPIN, HARTMAN MAY, TEMMEM-BRAK, VISSER, VAN DE WALL and WOUDA 1971 (A289) 118
NIKKILA, MIETTINEN, VESENNE. and PELKONEN 1965 (435) 155, 153
NILZEN 1959 (141) 68, 6
NIMALASURIYA, WIMALARATNE and THENABADU 1971 (A 49) 27
NIMALASURIYA, WIMALARATNE and THENABADU 1971 (90) 58
NIZET and ROBERTSON 1971 (349) 124, 123
NOBREGA, OXMAN, CONOLLY, ELVEBACK,

1005050861

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OBERMAN, HARLAN, SMITH, and GRAYBIEL 1969 (640) 205, 204
OBERMAN, LANE, HARLAN, GRAYBIEL and MITCHELL 1967 (A 549) 195
OBERWITTLER 1968 (211) 87, 82
OCAMPO OTERO 1964 (S 76) 329
OCHSNER 1968 (S 98) 330
OCHSNER and DAMRAU 1970 (A 649) 226
OCHSNER and DeBAKEY 1939 (A 190) 52
OETTEL 1969 (S 211) 337
OETTEL 1969 (S 53) 327
OGSTON and FULLERTON 1965 (A 618) 200
OGSTON, BENNETT and OGSTON 1970 (698) 218, 215
OJIAMBO 1968 (366) 128, 127
OLBERT 1955 (S 128) 332
OLDHAM 1964 (142) 68, 65
OLIVER 1966 (A 235) 102
OLIVER 1970 (699) 218, 217
OLIVER 1971 (367) 128, 126
OLIVER 1965 (A 366) 141
OLSEN 1968 (143) 68, 63
OLSON 1968 (A 438) 146
OLWIN and KOPPEL 1967 (A 619) 200
OPSTAD 1963 (S 138) 332
ORAM 1968 (S 100) 330
ORAM and SOWTON 1962 (27) 20, 18, 350(b)
ORAM and SOWTON 1963 (28) 20, 18, 15
ORAM and SOWTON 1963 (46) 25, 21
ORLOVA 1971 (700) 218, 214
ORTNER 1911 (29) 20, 15
OSBORN and GOLDSTEIN 1968 (434) 155, 153
OSKI, GOTTLIEB, MILLER and DELIVORIA-PAPADOPOULOS 1970 (1158) 320, 315
OSTER 1972 (S 322) 346, 463(a)
OSTER 1972 (S 321) 346
OSTFELD 1967 (A 210) 54
OSTFELD 1967 (A 403) 143
OSTFELD, SHEKELLE, TUFO, KILBRIDGE DRORI and KLAWANS 1971 (168) 72, 70
OSTRANDER 1968 (A 367) 141
OSTRANDER 1970 (A 368) 141
OTINIANO ORDONEZ 1967 (A 167) 51
OTIS 1970 (1159) 320, 316
OTT, KAULBACH and TERSIDES 1962 (A 739) 261
OVERHOLT 1963 (S 193) 336
OXMAN, CONNOLLY, NOBREGA, ELVEBACK, TITUS and KURLAND 1972 (A 50) 28
PACHINGER, HELLEBERG and BING 1972 (918) 273, 270
PAFFENBARGER 1970 (S 159) 334
PAFFENBARGER 1972 (A 369) 141
PAFFENBARGER and WILLIAMS 1966 (171) 73, 71
PAFFENBARGER and WING 1967 (172) 73, 71
PAFFENBARGER and WING 1969 (244) 94, 89
PAFFENBARGER and WING 1971 (173) 73, 71
PAFFENBARGER and WING 1972 (436) 155, 153
PAFFENBARGER, GIMA, LAUGHLIN and BLACK 1971 (169) 72, 70, 463 (a)
PAFFENBARGER, LAUGHLIN, GIMA and BLACK 1970 (170) 73, 70, 410 (a)
PAFFENBARGER, WOLF, NOTKIN and THORNE 1966 (481) 173, 163
PAFFENBARGER, NATKIN, KRUEGER, WOLF, THORNE, LeBAUER and WILLIAMS 1966 (245) 94, 89
PAGE 1971 (S 216) 338
PAGE and ALVAREZ 1967 (S 199) 337
PAGE, LEWIS and MOINUDDIN 1959 (841) 249, 246
PAGE, STARE, CORCORAN, POLLACK and WILKINSON 1957 (A 578) 197
PALMA 1963 (570) 181, 167
PANDLEY 1970 (564) 181, 167
PAPACOSTAS and REED 1966 (881) 268, 265
PAPADOPOULOS 1968 (A 261) 117
PAPP and SOLTI 1959 (880) 268, 265
PARADE 1968 (A 491) 190
PARAS CHAVERO, MERCADO CONTRERAS and QUINTERO NOVELLA 1970 (59) 38, 37
PARAS CHAVERO, MERCADO, and QUINTERO 1971 (60) 38, 37
PARDEE 1921 (30) 20, 17
PARKES, BENJAMIN and FITZGERALD 196 (A 505) 191
PARMEGGIANI and GILARDI 1952 (1005) 290, 288
PARMEGGIANI and GILARDI 1952 (1035) 298, 297
PARNELL 1951 (S 126) 332
PASAMONTES 1967 (A 168) 51
PASINI 1969 (A 262) 117
PASQUAZZI 1968 (A 15) 12
PASQUAZZI 1971 (A 263) 117
PAUL 1963 (A 85) 30
PAUL 1963 (S 39) 326
PAUL 1968 (S 99) 330
PAUL 1968 (S 101) 330
PAUL 1970 (329) 113, 112
PAUL 1971 (642) 205, 204
PAUL and OSTFELD (641) 205, 204
PAUL, MacMILLAN, McKEAN and PARK 1968 (437) 156, 154
PAUL, LEPPER, PHELAN, DUPERTUIS, MacMILLAN, McKEAN and PARK 1963 (246) 94, 90
PAULUSSEN 1970 (368) 128, 126
PAUN 1964 (S 42) 326
PAVITT 1968 (S 202) 337
PAVLIK and CERMAKOVA 1964 (A 470) 189
PAWINSKI 1914 (31) 20, 17
PEABODY 1962 (S 187) 336
PEDIATRIA DE ACTUALIDAD 1969 (S 287) 343
PELL and D'ALONZO 1958 (466) 172, 162
PELL and D'ALONZO 1961 (643) 205, 204
PELL and D'ALONZO 1970 (467) 172, 162
PEMBERTON and MACLEOD 1956 (482) 173, 163

1005050862

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PENNSYLVANIA MEDICAL JOURNAL 1964 (S 268) 342
PENNSYLVANIA MEDICAL JOURNAL 1964 (S 269) 342
PENNSYLVANIA MEDICINE 1966 (S 274) 342
PENTECOST and SHILLINGFORD 1964a (47) 25, 24
PENTECOST and SHILLINGFORD 1964a (757) 237, 230
PENTECOST and SHILLINGFORD 1964b (48) 25, 24
PENTECOST and SHILLINGFORD 1964b (758) 238, 230
PERNOD 1970 (A 483) 190
PERRELLI, PREVOT and SULOTTO 1970 (1160) 320, 316
PERRIN, KRUT and BRONTE-STEWART 1961 (450) 159, 157
PETERS and HALES 1965 (438) 156, 153
PETERSEN, SIGGAARD-ANDERSEN, KRISTENSEN and KJELDSEN 1968 (1114) 313, 308
PETROVIC 1970 (1161) 320, 316
PFEIFFER, BECK and GOLDSTEIN 1967 (A 756) 262
PFLANZ and BRUGGEMANN 1972 (A 439) 146
PHILADELPHIA MEDICINE 1968 (S 242) 341
PICCINELLI 1954 (A 236) 102
PICK 1967 (A 133) 47
PICKERING and SANDERSON 1944 (32) 20, 17
PILGERAM and PICKART 1968 (A 620) 200, 403(a)
PINCHERLE 1971 (673) 212, 207
PINCHERLE and SHANKS 1967 (1162) 320, 316
PINCHERLE and WRIGHT 1967 (A 237) 102
PINCHERLE and WRIGHT 1967 (674) 212, 209
PIRNAY, DEROANNE, DUJARDIN and PETIT 1971 (1072) 307, 302
PIRNAY, DUJARDIN DEROANNE and PETIT 1971 (1073) 307, 302
PLATT 1964 (S 77) 329
PLEASANTS, GRUGAN, RATLIFF 1966 (410) 150, 149
PLENGE 1930 (S 15) 324
POLLOCK 1956 (A 86) 30
PORSTEINSSON, HARDASON and SAMUELSSON 1966-1968 (61) 38, 36
PORTUGAL ALVAREZ, PEREZAGUA CLAMAGIRAND, AREVALO ALONSO and VELASCO MARTIN 1972 (675) 213, 210
POSEN 1968 (A 457) 188
POTAIN 1885 (S 3) 323
POZNER and BILLIMORIA 1970 (676) 213, 209
PRATT 1951 (A 191) 52
PRATT 1957 (A 410) 144
PREROVSKA and DRDKOVA 1967a (1115) 313, 310, 467(a)
PREROVSKA and DRDKOVA 1967b (1116) 313, 310
PREROVSKA and DRDKOVA 1971 (1117) 313, 310, 467(a)
PRESCOTT 1962 (S 68) 328
PRESTON 1929 (A 650) 226
PREUSS, EDER and WELLER 1970 (144) 69
PUBLIC HEALTH REPORTS 1965 (S 233) 339
PUBLIC HEALTH REPORT 1968 (S 249) 340
PUDDU and MENOTTI 1966 (A 238) 102
PUDDU and MENOTTI 1969 (577) 168
PUNSAR 1971 (A 477) 189
PUNSAR 1971 (S 119) 331
PUNSAR 1972 (A 478) 189
PUNSAR and KARVONEN (A479) 189
PUNSAR and PYORALA 1970 (525) 178, 165
PUNSAR and PYORALA 1970 (A 480) 189
PUNSAR, KARVONEN and PYORALA 1969 (524) 178, 165
PURI and BING 1967 (919) 273, 271
PURI, ALAMY and BING 1968 (920) 273, 271
PYORALA, KARVONEN, TASKINEN, TAKKUNEN, KYRONSEPPA, and
PELTOKALLIO 1967 (411) 150, 149
QUARTERLY JOURNAL OF MEDICINE 1965 (S 271) 342
RAAB 1960 (A 411) 144
RAAB 1964 (A 550) 195
RAAB 1965 (S 45) 326
RAAB 1967 (A 370) 141
RAAB 1969 (A 264) 117
RAAB and KRZYWANEK 1965 (A 551) 195
RAAB MARCHET and DEMING 1960 (759) 238, 228
RABINOWITSCH 1922 (A 651) 226
RAFFLE 1970 (A 506) 191
RAKUSAN, de ROCHEMONT, HANLON, BRAASCH, TSCHOPP, and BING 1967 (937) 276, 275
RAKUSON, de ROCHEMONT, HANLON, BRAASCH, TSCHOPP and BING 1968 (921) 273, 270
RALLI and OPPENHEIMER 1928 (145) 69, 63
RAMIREZ and GARCIA-PONT 1969 (A 579) 197
RAMSEY 1972 (1036) 298, 296
RAMSEY 1969 (1163) 320, 316
RANKIN, HALES WILKINSON, O'DAY, SANTAMARIA and BABARCZY 1969 (289) 100, 98
RAPPAPORT, REZNIKOFF, GLUECK, HONEYMAN and EISENBERG 1968 (396) 136, 134
RATCLIFFE 1965 (760) 238, 234
RAVENHOLT 1964 (S 141) 333
RAVENHOLT 1965 (S 82) 329
RAZDAN, SINGH and SRIVASTAVA 1967 (146) 69, 65
READER 1967 (A 371) 141
RECINE and CHIAVARO 1969 (412) 150, 149
RECKZEH and DONTENWILL 1970 (1164) 320, 316

100505863

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

REDAKSIE 1967 (A 311) 120
REDGRAVE 1972 (S 177) 335
REECE and BALL 1972 (761) 238, 233
REGAN, FRANK, McGINTY, ZOBL, HELLEMS and BING 1961 (762) 238, 231, 350(a)
REGAN, HELLEMS and BING 1960a (764) 238, 231
REGAN, MARTIN, FRANK, McGINTY, HELLEMS and BING 1960b (763) 238, 231
REHDER and ROTH 1959 (842) 249, 247
REID 1958 (S 66) 328
REID 1960 (A 265) 117
REID 1968 (S 203) 337
REID 1969 (A 51) 28
REID 1972 (A 652) 226
REID, CORNFIELD, MARKUSH, and SEIGEL 1966 (331) 113, 112
REID, HOLLAND, HUMBERFELT and ROSE 1966 (548) 180, 166
REID, HOLLAND and ROSE 1967 (330) 113, 111
REIMER and TISO 1971 (500) 176, 164
REIMER, TISO and HERRLEIN 1969 (147) 69, 63
REINIS, BAZIKA, KUTHAN, SLABY, REISENAUER and MARKIOVA 1970 (A 472) 189
REINIS, POKORNY, JORAKOVA, KLENKA, KRAUS, REISENAUER and MARSIKOVA 1970 (A 192) 52
REISSELL, HAGOPIAN and HATCH 1965 (A 581) 197
RENTCHNICK 1962 (S 189) 336
REUSE and BOURGAIN 1960 (A 685) 256
REVOTSKIE, KANNEL, GOLDSMITH and DAWBER 1962 (212) 87, 81
RICHARD, LELOUCH, CLAUDE and SCHWARTZ 1969 (677) 213, 209
RICHARDSON 1971 (460) 171
RICHARDSON 1972 (439) 154
RICHARDSON, WALKER and WALKER 1965 (S 144) 333
RIESMAN and HARRIS 1934 (290) 100, 97
RIGDON 1960 (S 132) 332
RIGDON 1962 (S 137) 332
RILEY, OBERMAN, LAMPTON and HURST 1970 (413) 150, 149
RIME and MERTENS (A 312) 120
RIME and MERTENS 1970 (A 484) 190
RINGLOD, GOLDSMITH, HELWIG, FINN and SCHUETTE 1962 (1037) 299, 295
RINSLER 1967 (A 440) 146
RIPKA 1968 (A 471) 189
RISEMAN 1966 (A 87) 30
RISSANEN, PYORALA and HEINONEN 1972 (91) 58
RIVAL and MATHES 1969 (992) 273, 270
RIVIER 1966 (A 88) 30
ROBB and MARKS 1964 (A 412) 144
ROBB and JABS 1968 (A 621) 200
ROBERTS and LLOYD 1972 (A 507) 191
ROBIN, RAVENS and BING 1969 (1074) 307, 300
ROBIN, RAVENS and BING 1969 (882) 268, 265
RODE and SHEPHARD 1971 (A 653) 226
ROGERS 1965 (303) 106, 105
ROMBERG 1925 (33) 20, 15
ROMERO and TALESNIK 1967 (A 686) 256
ROMO 1972 (527) 178, 165
ROMSLO 1971 (678) 213, 210
ROSE 1962 (A 508) 191
ROSE 1964 (380) 133, 130
ROSE 1969 (A 413) 144
ROSE 1970 (A 372) 141
ROSE, AHMETELI, CHECCACCI, FIDANZA GLAZUNOV, DE HAAS, HORSTMANN, KORNITZER, MELONI, MENOTTI, VAN DER SANDE, DE SOTO-HARTGRE PISA and THOMSEN 1968 (332) 113, 112
ROSE and BLEASA 1970 526(a)
ROSENBERG 1968 (1038) 299, 296
ROSENBERG 1971 (1039) 299, 296
ROSENBERG 1972 (1040) 299, 296
ROSENKRANZ 1966 (A 52) 28
ROSENKRANZ 1967 (A 53) 28
ROSENMAN 1965 (A 313) 120
ROSENMAN 1967 (A 314) 120
ROSENMAN 1967 (A 315) 120
ROSENMAN 1968 (247) 94, 90
ROSENMAN 1971 (397) 136, 134
ROSENMAN and FRIEDMAN 1961 (369) 128, 127, 126
ROSENMAN and FRIEDMAN 1963 (679) 213, 207
ROSENMAN, FRIEDMAN, JENKINS and STRAUS 1968 (251) 94, 90
ROSENMAN, FRIEDMAN, JENKINS, STRAU WURM and KOSITCHEK 1966 (A 580) 197
ROSENMAN, FRIEDMAN, JENKINS, STRAU WURM and KOSITCHEK 1967a (248) 94, 90
ROSENMAN, FRIEDMAN, JENKINS, STRAU WURM and KOSITCHEK 1967b (249) 94, 90
ROSENMAN, FRIEDMAN, JENKINS, STRAU WURM and KOSITCHEK 1967c (250) 94, 90
ROSENMAN, FRIEDMAN STRAUS, JENKINS ZYZANSKI and WURM 1970 (252) 94, 90
ROSENMAN, FRIEDMAN, STRAUS, WURM, JENKINS and MESSINGER 1966 (253) 94, 90
ROSENMAN, FRIEDMAN, STRAUS, WURM, KOSITCHEK, HAHN and WERTHESSEN 1964 (680) 213, 207
ROSKRAMM 1964 (1075) 307, 303
ROSS and BLESA 1970 (923) 273, 271
ROSS and IVY 1946 (S 21) 324
ROSSI-FANELLI and ANTONINI 1958 (1165) 320, 315
ROTH 1960 (S 33) 325
ROTH and SCHICK 1958 (S 29) 325

1005050864

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ROTH and SHICK 1960 (804) 243, 241
ROTH and SHICK 1960 (805) 243, 240
ROTH, BERKI and WOLFF 1967 (350) 125, 123, 122
ROTH and PEPE 1957 (351) 125, 123, 122
ROTHERMICH 1965 (S 145) 333
ROTTENSTEIN, PEIRCE, RUSS, FELDER and MONTGOMERY 1960 (938) 276, 275
ROUCH, RIOUFOL and BOURBON 1971 (1006) 294, 289
ROWE 1966 (A 31) 14
ROWE, THOMSEN, STENLUND, McKENNA, SIALER and CORLISS 1969 (A 32) 14
ROWSELL, HEGARDT, DOWNIE, MUSTARD and MURPHY 1966 (979) 284, 282
ROYSTON 1972 (70) 42, 40
RUDOLPH, DIEZEL, SEBENING and DIETZE 1968 (A 740) 261
RUDOLPH, DIEZEL, SEBENING and DIETZE 1968 (A 741) 261
RUEL and BARTHE 1954 (1007) 294, 290
RUHL and LIN 1936 (1041) 299, 296
RUHL and LIN 1936 (1008) 294, 290
RUIKKA, SOURANDER and KASANEN 1966 (518) 178, 165
RUIZ, FIGUEROA, HORNA and PENALOZA 1969 (593) 183, 169
RUSSEK 1958 (A 316) 120
RUSSEK 1959 (381) 133, 130
RUSSEK 1960 (306) 106, 105
RUSSEK 1961 (305) 106, 105
RUSSEK 1962 (A 317) 120
RUSSEK 1964 (398) 136, 134
RUSSEK 1965 (304) 106, 105
RUSSEK 1967 (A 89) 30
RUSSEK 1967 (A 319) 120
RUSSEK 1967 (A 318) 120
RUSSEK 1971 (A 90) 30
RUSSEK 1972 (A 320) 120
RUSSEK and ZOHMAN 1955 (765) 238, 229
RUSSEK and ZOHMAN 1958 (484) 173, 163, 351(a)
RUSSEK, ZOHMAN and DORSET 1955 (766) 238
RUSSEK, ZOHMAN and DORSET 1955 (34) 20, 17
RUSSO 1968 (A 54) 28
RUSSO 1968 (A 520) 192
SACKETT 1969 (S 107) 330
SACKETT and WINKELSTEIN 1965 (A 266) 117
SACKETT, GIBSON, BROSS and PICKREN 1968 (92) 58, 56
SACHDEV and WAHI 1961 (S 36) 326
SAIGER 1966 (S 323) 346, 357(a)
SAILAPATHY 1966 (A 169) 51
SALA 1963 (A 55) 28
SALATICH 1965 (A 757) 262
SALBER and MACMAHON 1961 (399) 137, 134
SALTER 1967 (S 149) 333
SAMANEK and AVIADO 1966 (883) 268, 266
SANTRUCEK 1969 (A 475) 189
SANTRUCEK 1970 (514) 177, 165
SANTRUCEK and VACEK 1967 (A 473) 189
SANTRUCEK and VACEK 1968 (A 474) 189
SANTRUCEK and VACEK 1968 (S 54) 327
SAPHIR, OHRINGER and SILVERSTONE 1956 (A 291) 118
SAPHIR and RAPAPORT 1969 (939) 276, 275
SARTWELL 1971 (701) 218, 216
SARTWELL, MASI, ARTHES, GREENE and SMITH 1969 (702) 218, 216
SARVOTHAM and BERRY 1968 (563) 181, 16
SCHAR 1969 (A 267) 117
SCHAR 1969 (A 373) 141
SCHAR 1970 (A 492) 190
SCHATTENBERG 1968 (S 204) 337
SCHEIDT, ASCHEIM and KILLIP 1970 (78) 44, 43
SCHETTLER 1966 (A 374) 141
SCHETTLER 1969 (A 134) 47
SCHETTLER 1970 (A 170) 51
SCHETTLER 1972 (A 494) 191
SCHETTERL and HILD 1967 (A 493) 190
SCHEUER and STEZOSKI 1968 (A 687) 256
SCHIEVELBEIN and EBERHARDT 1972 (1076) 307, 300
SCHIEVELBEIN and EBERHARDT 1972 (S 63) 327
SCHIEVELBEIN and SCHIRREN 1964 (980) 284, 282
SCHIEVELBEIN and WERLE 1967 (884) 268, 264
SCHIEVELBEIN, PETER, TRAUTSCHOLD and WERLE 1966 (A 622) 200
SCHIEVELBEIN, LONDONG, LONDONG, GRUMBACH, REMPLIK, SHAUER and IMMICH 1970 (955) 279, 277
SCHILLING 1969 (A 268) 117
SCHILLING, CHRISTAKIS, BENNETT and COYLE 1964 (A 582) 197
SCHIMMLER and NEFF 1966 (56) 35, 34
SCHIMMLER and NEFF 1966 (533) 179, 165
SCHIMMLER and NEFF 1968 (A 56) 28
SCHIMMLER, NEFF and SCHIMERT 1968 (534) 179, 165
SCHIMMLER, SCHIMERT and NEFF 1967 (148) 68, 60
SCHIRGER and SHICK 1964 (S 43) 326
SCHMAUSS and ARIT 1970 (A 193) 52
SCHMIDT 1965 (S 83) 329
SCHMIDT 1939 (1009) 294, 290, 289, 280
SCHMIDT 1939 (1042) 299, 297
SCHMIDT 1940 (1010) 294, 290
SCHMIDT 1940 (1043) 299, 297
SCHMIDT 1938 (A 171) 51
SCHMIDT 1972 (A 465) 188
SCHMITERLOW, HANSSON, ANDERSSON, APPELGREN and HOFFMANN 1967 (A 758) 262
SCHNEIDER 1938 (A 654) 226
SCHOENBERGER 1970 (S 324) 346
SCHOENBERGER, STAMLER, LINDBERG, SHEKELLE, STOKER 1969 (A 269) 117

10050865

Source: https://www.industrydocuments.ucsf.edu/docs/xzk0000

SCHOENDORF, WILKENING and CLIFFTON 1970 (860) 252, 250
SCHOR, ELSOM, ELSOM and DUNN 1964b (255) 94, 89, 360(a)
SCHOR, CLARK, PARKHURST, BAKER and ELSOM 1964a (254) 94, 89
SCHRENK 1942 (1011) 294, 290, 289, 288
SCHULTHEISS 1969 (A 496) 191
SCHUMANN 1968 (S 102) 330
SCHUMANN 1971 (A 655) 226
SCHUSTER 1966 (A 495) 191
SCHWARTZ, RICHARD, LELLOUCH and CLAUDE 1971 (681) 213, 207
SCHWARTZ, LELLOUCH, ANGUERA, BEAUMONT and LENEGRE 1966 (57) 35, 33
SCHWARTZ, LELLOUCH, ANGUERA, RICHARD and BEAUMONT 1965 (149) 68, 63
SCHWARTZ, ROSENWEIG, TOOR and LEWITUS 1963 (A 583) 197
SCHWEIZER, PLANTA, BATCHELET and PLETSCHER 1960 (924) 273, 271
SCHWEIZER 1969 (S 57) 327
SCHWEIZERISCHE MEDIZINISCHE WOCHENSCHRIFT 1971 (S 291) 343
SCOTT 1940 (A 656) 226
SCOTT 1952 (S 23) 325
SEBRELL 1968 (A 441) 146
SEFTEL, KEW and BERSOHN 1970 (599) 184, 169
SEFTEL, KEELEY, WALKER, THERON and DE LANGE 1965 (598) 184
SEGERS and MERTENS 1972 (400) 137, 135
SEIGEL and LONCIN 1968 (71) 42, 40
SELTZER 1968 (S 325) 346, 382(a)
SELTZER 1970 (S 326) 346, 425(a)
SELTZER 1971 (S 168) 334, 470(a)
SELTZER 1972 (S 123) 331, 416(b)
SELTZER 1972 416(i)
SELTZER 1973 (S 182) 335, 439(a)
SERAFIMOVA 1971 (767) 238, 228
SHAFFER 1964 (A 172) 51
SHAH 1968 (A 173) 51
SHANKS 1966 (885) 268, 265
SHANOFF 1965 (A 375) 141
SHAPIRO, WEINBLATT, FRANK and SAGER 1965 (257) 95, 89
SHAPIRO, WEINBLATT, FRANK and SAGER 1969 (256) 94, 89
SHAPIRO, WEINBLATT, FRANK and SAGER 1970 (490) 174, 163
SHAPIRO, WEINBLATT, FRANK, SAGER and DENSEN 1963 95, 89
SHARMAN, VANOV and VOGT 1962 (A 742) 261
SHEKELLE 1968 (461) 160
SHEKELLE and OSTFELD 1963 (S 139) 332
SHEKELLE, OSTFELD and PAUL 1969 95, 90
SHEPHERD 1951 (806) 243, 241
SHIBATA, HOLLANDER and WEBB 1968 (886) 268, 265
SHIELDS 1971 (1044) 299, 296
SHILLINGFORD 1965 (49) 25, 24
SHIMAMOTO and ISHIOKA 1963 (981) 284, 2
SHLESER 1965 (A 91) 30
SIBLEY 1965 (A 112) 31
SIDD, KEMP and GORLIN 1970 (352) 125, 12
SIDD, SASAHARA and LITTMANN 1966 (325) 110, 108
SIEBECK 1935 (A 194) 52
SIEBELT 1917 (S 10) 323
SIEDEK 1971 (A 148) 49
SIEVERS 1967 (261) 95, 90
SIEVERS 1968 (260) 95, 90
SIEVERS, EDWARDS, MURRAY and SCHRENK 1942 (1012) 294, 290
SIGGAARD-ANDERSEN, KJELDSEN, PETERSEN and ASTRUP 1967 (1118) 313, 309
SIGGAARD-ANDERSEN, PETERSEN, HANSEN and MELLEMGAARD 1968 (1119) 313, 309
SIGGAARD-ANDERSEN, PETERSEN, HANSEN and MELLEMGAARD 1969 (1120) 313, 308
SIGLER 1955 (S 26) 325
SIGURJONSSON 1969 (566) 181, 167
SILVETTE, LARSON and HAAG 1961 (A 715) 258
SIMBORG 1970 (A 270) 117
SIMON and IGLAUER 1960 (768) 238, 229
SIMON and IGLAUER 1961 (769) 238, 229
SINGER 1935 (A 657) 226
SINGH 1971 (565) 181, 167
SINGH, KHANNA, SRIVASTAVA and HOON 1970 (A 57) 28
SINGH 1965 (984) 285, 282
SINGH and OESTER 1964a (982) 284, 283
SINGH and OESTER 1964b (983) 284, 283
SIRTORI 1967 (S 90) 329
SIVE, MEDALIE, KAHN, NEUFELD and RISS 1971 (A 553) 195
SJOVALL and WIHMAN 1934 (79) 44, 43
SLABY, BAZIKA, REISENAUER and MARSIKOVA 1970 (A 552) 195
SLANY 1972 (A 554) 195
SLATER 1950 (1077) 307, 303
SLEIGHT 1964 (887) 268, 265
SMITH 1943 (35) 20, 15
SMITH and SMITH 1962 (A 16) 12
SMITH 1937 (307) 106
SMITH 1967 (A 509) 191
SMYTH, ADEY and LANGLEY 1970 (682) 213, 210
SNEGIREFF and LOMBARD 1963 (308) 106, 105
SODI-PALLARES, DE MICHELI, MEDRANO FISHLEDER, BISTENI, FRIEDLAND, an TESTELLI 1962 (A 92) 30
SOEHREN 1948 (A 174) 51
SOGANI and JOSHI 1965 (861) 252, 250
SOLBERG 1971 (A 530) 193

1005050866

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

SOLOFF and POWERS 1964 (770) 238, 230
SOLOFF and SCHWARTZ 1963 (A 584) 197
SOLOFF and SCHWARTZ 1966 (683) 213, 207
SOLTI, KRASZNAI, REV and NAGY (941) 276, 275
SOLTI, ISKUM, ZOLTAN, PAPP and PREISICH 1964 (925) 273, 271
SOLTI, PETER, OLAH, ISKUM, REV, HERMANN and REFI 1963 (940) 276, 275
SOLVSTEEN and KRISTJANSEN 1968 (1121) 313, 309
SOMMER 1972 (S 327) 346
SONNENBLICK, ROSS, COVELL, KAISER and BRAUNWALD 1965 (A 743) 261
SPAIN 1960 (291) 100, 98
SPAIN 1970 (62) 38, 37
SPAIN 1970 (63) 38, 37
SPAIN and NATHAN 1961 (684) 213, 209
SPAIN, BRADESS and HUSS (93) 58
SPAIN, NATHAN and GELLIS 1963 (A 585) 198
SPAIN, BRADESS, MATERO and TARTER 1969 (64) 38, 36, 427(a)
SPECKMANN, KIENSCH, MAETZEL and MAYER 1967 (A 17) 12
SPECTOR and SPAIN 1972 (A 58) 28
SPELMAN and LEY 1966 (549) 186, 166
SPINA, LISI, SILVIA and SIRAGUSA 1969 (A 543) 194
SPRAGUE 1958 (A 321) 120
SPITTLE 1972 (S 178) 335, 403(a)
SPRAGUE 1961 (A 322) 120
SPRAGUE 1966 (A 271) 117
STABLES, RUBENSTEIN, METZ and LEVIN 1967 (711) 221, 219
STALLWORTH, NAJIB and RAMIREZ 1967 (807) 243, 241
STAMLER 1959 (419) 152, 151
STAMLER 1959 (476) 173, 162
STAMLER 1962 (A 226) 77
STAMLER 1962 (A 555) 195
STAMLER 1962 (A 135) 47
STAMLER 1964a (262) 95, 90
STAMLER 1964b (263) 95, 90
STAMLER 1965 (A 586) 198
STAMLER 1967 (A 442) 146
STAMLER 1968 (264) 95, 90
STAMLER 1969 (A 379) 142
STAMLER 1970 (A 591) 198
STAMLER 1970 (A 592) 198
STAMLER 1971 (A 381) 142
STAMLER 1971 (A 380) 142
STAMLER and BERKSON 1972 (451) 159, 157
STAMLER, BERKSON, LINDBERG and LEVINSON 1966 (A445) 147
STAMLER, BERKSON, YOUNG, LINDBERG, HALL, MILLER, STAMLER 1962 (A 446) 147
STAMLER and EPSTEIN 1972 (A 382) 142
STAMLER, BERKSON, LINDBERG, MILLER HALL 1961 (477) 173
STAMLER, BERKSON, YOUNG, HALL, and MILLER 1963 (452) 159, 157
STAMLER, BERKSON, YOUNG, LINDBERG HALL, MOJONNIER and ANDELMAN 1963 (A 587) 198
STAMLER, BERKSON, LEVINSON, LINDBE MOJONNIER, MILLER, HALL and ANDELMAN 1966 (A 443) 146
STAMLER, BERKSON, LEVINSON, MOJONN EPSTEIN, HALL, BURKEY, SOYUGENE and ANDELMAN 1968 (A 444) 147
STAMLER, BERKSON, LINDBERG, MILLER SOYUGENC, TOKICH and WHIPPLE 1968 (A 589) 198
STAMLER, BERKSON, LINDBERG, HALL, MILLER, MOJONNIER, LEVINSON, DOHEN and YOUNG 1966 (A 377) 141
STAMLER, BERKSON, LINDBERG, HALL, MILLER, MOJONNIER, LEVINSON, COHEN and YOUNG 1966 (A 378) 141
STAMLER, HALL, MOJONNIER, BERKSON, LEVINSON, LINDBERG, ANDELMAN, MILLER and BURKEY 1966 (A 376) 141
STAMLER, LINDBERG, BERKSON, MILLER TEMPLETON and HALL 1960 (420) 152, 151
STAMLER, LINDBERG, BERKSON, SHAFFE MILLER and POINDEXTER 1960 (475) 173, 162
STAMLER, SCHOENBERGER, LINDBERG, SHEKELLE, STOKER, EPSTEIN, DeBOE STAMLER, RESTIVO, GRAY and CAIN 1969 (A 227) 77
STARR 1954 (627) 203, 202
STARR 1960 (771) 238, 228
STARR 1967 (772) 238, 228
STEAD 1969 (A 447) 147
STEAD 1969 (A 588) 198
STEBNER 1972 (A 383) 142
STEEDS 1969 (A 239) 102
STEFANOVICH, FORE, KAJIYAMA and IWANAGA 1969 (956) 279, 277, 432(a)
STEINMANN 1966 (A 211) 54
STEJFA 1967 (511) 177, 164
STEPHENS 1970 (A 458) 188
STEPHENS 1970 (A 459) 188
STERLING 1971 (S 328) 346, 461(a)
STERLING 1972 416(h)
STERN and BRAUN 1966 (889) 268, 266
STERN and RAPAPORT 1967 (890) 268, 265
STERN, FERGUSON and RAPAPORT 1964 (888) 268, 265
STEVENS 1917 (36) 20, 15
STEWART 1970 (A 228) 77
STOCKS 1969 (333) 113, 112
STORCH, ENGELMANN and KOHLER 1971 (536) 174, 165
STRAUBE 1966 (A 323) 120
STRAUBE and LAFRENZ 1966 (A 272) 117
STROBEL and GSELL 1965 (607) 184, 169
STOLLEY 1972 (A 149) 49
STROMBLAD 1959 (942) 276, 275, 438(a)
STRONG 1966 (94) 58
STRONG, RICHARDS, McGILL, EGGEN and McMURRY 1969 (95) 58

10050867

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

STUART-HARRIS 1962 (A 175) 51
STUBER 1967 (S 91) 329
SULZBERGER 1934 (150) 69, 62
SUMMERS, RICHMOND and WECHSLER 1971 (773) 238, 231, 480(a)
SUSSMAN, SHAFRIR and STEINBERG 1958 (967) 281, 280
SUZUKI 1969 (1078) 307, 303
SWAINE, PERLMUTTER and ELLIS 1964 (A 744) 261
SWARTOUT and WEBSTER 1940 (292) 100
SWARTZ 1971 (S 61) 327
SYME 1967 (293) 100, 98
SYME 1970 (A 384) 142
SYME 1965 (493) 174, 163
SYME, HYMAN and ENTERLINE 1964 (492) 174, 163
SZANTO 1966 (S 148) 333, 390(a)
SZANTO 1967 (S 150) 333, 390(a)
SZANTO and YUDKIN 1969 (A 623) 200
SZOLLOSI, MEDVE and JENEY 1970 (1079) 307, 300
TAGERT 1970 (843) 249, 247
TALBOTT 1964 (685) 213, 209
TAUBERGER 1964 (A 759) 262
TAYLOR, BLACKBURN, PUCHNER, VASQUEZ, PARLIN and KEYS 1969 (A 593) 198
TAYLOR and SCHILLING 1967 (A 510) 191
TAYLOR, CINGOLANI, GRAHAM and CLANCY 1967 (A 745) 261
TECULESCU, LILIS, HILT and ROVENTA 1972 (401) 137, 135
TERASLINNA, PARTENEN, KOSKELA and OJA 1971 (526) 178, 165
TERRIS 1964 (462) 171, 160
TERRIS 1968(S 103) 330
TERRY 1970 (S 120) 331
TERZIDIS, KAULBACH and OTT 1963 (A 240) 102
TEUSCHER (A 59) 28
THEIS 1965 (A 195) 52
THEODORE, O'DONNELL and BACK 1971 (1166) 320, 316
THEORELL and RAHE 1972 (A 324) 120
THIENES 1960 (957) 279, 277
THIENES, CANGELOSI and SKILLEN 1962 (A 716) 258
THISEUS and TIBBLING 1970 (A 18) 12
THOMAS 1958 (644) 206, 204
THOMAS 1959 (808) 243, 240
THOMAS 1959 (382) 133, 130
THOMAS 1960 (A 292) 118
THOMAS 1968 (383) 133, 131, 381(a)
THOMAS 1969 (A 327) 121
THOMAS, BATEMAN and LINDBERG 1956 (775) 239, 229
THOMAS and COHEN 1960 (A 594) 198
THOMAS, FARGO and ENSLEIN 1970 (402) 137, 134
THOMAS and GREENSTREET 1973 (A 325) 120
THOMAS and MURPHY 1958 (776) 239, 229
THOMAS and MURPHY 1960a (777) 239, 229
THOMAS and MURPHY 1960b (778) 239, 229
THOMAS and ROSS 1968 (A 326) 120
THOMAS, ROSS and HIGINBOTHOM 1964 (645) 206, 204
THORNE, WING and PAFFENBARGER 1968 (265) 95, 89
THOULD 1965 (353) 125, 122
TIBBLIN 1967 (646) 206, 204
TIBBLIN 1968 (602) 184, 169
TIBBLIN 1970 (601) 184, 169
TIBBLIN 1970 (A 385) 142
TIBBLIN 1971 (1080) 307, 300
TIBBLIN and WILHELMSEN 1970 (S 112) 331
TIBBLIN and WILHELMSEN 1971 (603) 184, 169
TIBBLIN and WILHELMSEN 1971 (604) 184, 169
TILLER, SCHILLING and MORRIS 1968 (A 511) 192
TKACHENKO, TISHCHENKO, ZATSEPILIN and DIMITROVA 1966 (1167) 320, 316
TOBIASCH 1951 (774) 239, 228
TOMATIS, FIERENS and VERBRUGGE 1972 (151) 69, 63
TONELLI, TUMIOTTO, BISBINI, PRONTICELLI and MONTI 1968 (A 136) 47
TORKELSON 1964 (A 113) 31
TRAVELL, RINZLER and KARP 1960 (926) 273, 271
TRINDER and HARPER 1962 (1013) 294, 290
TRUETT, CORNFIELD and KANNEL 1967 (213) 87, 82
TRUHAUT, BOUDENE and CLAUDE 1968 (1168) 320, 316
TRUHAUT, BOUDENE and CLAUDE 1968 (1122) 313, 309
TRULSON, CLANCY JESSOP, CHILDERS and STARE 1964 (384) 133, 131
TSUJIMOTO, TANINO and KUROGOCHI 1965 (968) 281, 280
TUOHY 1943 (A 448) 147
TURNER and ILLINGWORTH 1971 (S 169) 33
TURPEINEN, MIETTINEN, KARVONEN, ROINE, PEKKARINEN, LEHTOSUO and ALIVIRTA 1968 (A 449) 147
TURPEINEN, MIETTINEN, KARVONEN, ROINE, PEKKARINEN, LEHTOSUO and ALIVIRTA 1969 (A 590) 198
TYROLER and CASSEL 1964 (491) 174, 163
TZAGOURNIS and REYNERTSON 1972 (294) 100, 98
UDRY 1971 (S 121) 331
UNVERRICHT 1941 (152) 69, 63
USTVEDT 1959 (A 212) 54
VALIC and DURIC 1954 (1014) 294, 290
VALLIN 1883 (S 2) 323
VALORI, INNOCENTI, SORBINI and SOLINA 1964 (927) 273, 271
VAN BUCHEM 1967 (A 450) 147, 383(a)
VAN BUCHEM 1970 (588) 183, 168
VAN BUCHEM, DRION, WIGBOUT and BOSSCHIETER 1970 (A 544) 194

1005050868

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

VAN BUCHEM, DRION, WIGBOUT, BOSSCHIETER and FRIMA 1970 (628) 203, 201
VAN HOUTE and KESTELOOT 1972 (686) 213, 209
VAN ITALLIE 1962 (A 137) 47
VAN LIEW 1968 (1123) 313, 308
VAN LIEW 1968 (1124) 313, 308
VAN LIEW 1970 (1125) 314, 309
VAN REENEN 1954 (S 24) 325
VAN VOORST VADER 1965 (585) 182, 168
VEITH 1940 (1081) 307
VELA 1967 (S 200) 337
VERESS 1965 (A 688) 256
VESSEY and DOLL 1968 (703) 218, 216
VIEL, DONOSO and SALCEDO 1968 (96) 58
VILLIGER and HEYDEN-STUCKY 1966 (58) 35, 33
VLAICU, MACAVEI and PATIU 1971 (687) 213, 210, 478(a)
VLAICU, MACAVEI and PATIU 1971 (A 595) 198
VOGEL and GLESER 1972 (1082) 307, 302
VOGEL, GLESER WHEELER and WHITTEN 1972 (1083) 307, 302
VOGEL, JACOBWITZ and CHIDSEY 1969 (A 746) 261
VON AHN 1948 (A 658) 226
VON AHN 1949 (S 21) 324
VON AHN 1960 (37) 20, 16
VON HOLST 1970 (A 93) 30
VUJADINOVIC 1965 (A 196) 52
VUKADINOVIC and SARIC 1966 (616) 185, 170
VYTILLINGAM (555) 180, 166
WAHLBERG 1962 (440) 156, 153
WAKEHAM 1972 (S 179) 335
WAKELEY 1964 (S 142) 333
WAKERLIN 1966 (A 274) 117
WALDEN, SCHAFFE, LEMON, SUNSHINE and WYNDER 1964 (A 596) 198
WALKER 1966 (S 329) 346
WALKER 1968 (A 451) 147
WALKER 1969 (385) 133, 130
WALKER 1969 (A 386) 142
WALKER 1969 (S 156) 333
WALKER 1969 (A 452) 147
WALKER and BERSOHN 1969 (A 387) 142
WALKER 1971 (441) 156, 154
WALKER and GREGORATOS 1967 (354) 125, 123, 122
WANSTRUP, KJELDSEN and ASTRUP 1969 (1126) 314, 309
WARDWELL, HYMAN and BAHNSON 1968 (A 328) 121
WARKENTIN 1968 (A 273) 117
WARREN 1962 (A 19) 13
WARREN 1965 (A 60) 28
WARSHAW 1969 (A 388) 142
WARTER, SACREZ and BRECHENMACHER 1972 (531) 178, 165
WATSON, BUCHANAN and DICKSON 1963 (688) 213, 207
WATTS 1966 (A 717) 258
WEBB, WAX and SUGG 1968 (891) 268, 265
WEGMANN 1967 (A 275) 117
WEGRIA 1951 (928) 274, 270
WEINBLATT, FRANK, SHAPIRO and SAGER 1968a (266) 95, 89
WEINBLATT, SHAPIRO and FRANK 1971 (A 659) 226
WEINBLATT, SHAPIRO, FRANK and SAGER 1968b (267) 95, 89, 399(a)
WEINER, DRASKOCZY and BURACK 1962 (A 718) 258
WEINROTH and HERZSTEIN 1946 (442) 156, 153
WEINSTEIN, EPSTEIN and THE WORKING SUBCOMMITTEE ON CRITERIA AND METHODS, COMMITTEE ON EPIDEMIOLOGICAL STUDIES, AMERICA HEART ASSOCIATION 1964 (295) 100, 9
WEIR and DUNN 1970 (268) 95, 91
WEISS, SLAWSKY and DESFORGES 1971 (1015) 294, 291
WEISS 1972 (153) 69, 61
WEISSBACH, SCHOPEN and LANGE 1970 (A 61) 28
WEISSLER, KRUGER, BABA, SCARPELLI, LEIGHTON and GALLIMORE 1968 (A 689) 256
WELBORN, BRECKENRIDGE, RUBENSTEIN DOLLERY and FRASER 1966 (443) 156, 153
WELBORN, CUMPSTON, CULLEN, CURNOW McCALL and STENHOUSE 1969 (498) 176, 164
WELLS 1969 (A 460) 188
WENNESLAND 1945 (1016) 294, 290
WENZEL 1967 (895) 269
WENZEL, MacCARTHY and RUTLEDGE 1964 (892) 268, 265
WENZEL and RICHARDS 1970 (985) 285, 202
WENZEL and RICHARDS 1970 (896) 269, 265
WENZEL and STARK 1965 (893) 269, 265
WENZEL and STARK 1966 (894) 269, 265
WENZEL, TURNER, JORDAN and SINGH 1961 (969) 281, 280
WENZEL, TURNER and KISSIL 1959 (958) 279, 277, 432(a)
WENZEL, WATTANAPONGSIRI and VEDRAL 1964 (943) 276, 275
WERKÖ 1961 (A 535) 193,
WERKÖ 1971 (A 389) 142
WERLE and SCHIEVELBEIN 1965 (986) 285, 2
WERTLAKE, WILCOX, HALEY and PETERSON 1958 (689) 213, 207
WESSLER, MING S-C, GUREWICH and FREIMAN 1960 (A 197) 52
WEST, BELLET, MANZOLI and MÜLLER 1962 (930) 274, 270
WEST, SANTIAGO, GUZMAN and BELLET 1958 (929) 274, 270
WESTFALL 1965 (A 719) 259
WESTFALL 1967 (A 720) 259
WESTFALL, CIPOLLONI and EDMUNDOWIC

10050869

Source: https://www.industrydocuments.ucsf.edu/docs/pzlk0000

WESTFALL and WATTS 1961 (809) 243, 241
WESTFALL and WATTS 1962 (810) 243, 241
WESTFALL and WATTS 1963 (897) 264, 264
WESTFALL and WATTS 1964 (898) 269, 264
WHELAN 1968 (944) 276, 275
WHEREAT 1970 (1127) 314, 310
WHITAKER 1969 (A 276) 117
WHITE, GORE and LARKEY 1964 (970) 281, 280
WHITE 1933 (A 660) 227
WHITE 1935 (355) 125, 122, 123
WHITE 1957 (356) 125, 122
WHITE 1957 (S 184) 336
WHITE 1963 (S 69) 328
WHITE and SHARBER 1934 (A 661) 227
WHITEHEAD and WORTHINGTON 1961 (1045) 299, 296
WHYTE 1965 (421) 152, 151
WIDMER 1967 (A 138) 47
WIDMER 1972 (A 139) 47
WIDMER, HARTMANN, DUCHOSAL and PLECHL 1969 (154) 69, 65
WIDMER, HARTMANN, DUCHOSAL and PLECHL 1969 (A 277) 117
WILENS 1964 (S 78) 329)
WILENS and PLAIR 1962 (97) 58, 56
WILHELMSEN, ELMFELDT, TIBBLIN, VEDIN and WILHELMSEN 1972 (605) 184, 169
WILHELMSEN, GRIMBY, BJURE, EKSTROM-JODAL, AURELL and TIBBLIN 1969 (414) 150, 148
WILHELMSEN, TIBBLIN, EIMFELDT, SANNE, VEDIN and WILHELMSSON 1972 (A 391) 142
WILHELMSEN, TIBBLIN and WERKÖ 1972 (A 390) 142
WILLIAM-OLSSON 1965 (S 146) 333
WILLIAM-OLSSON 1965 (S 84) 329
WILLIAMS and WHITE 1961 (A 115) 32
WILSON and JOHNSTON 1939 (38) 20, 15
WILSON and JOHNSTON 1941 (629) 203, 201
WINK and HAGER 1972 (370) 128, 127
WITTENBERG 1966 (1169) 320, 315
WOLF 1969 (A 62) 28
WOLFERTH 1937 (A 176) 51
WOLFERTH 1945 (A 116) 32
WOLFF 1937 (A 662) 227
WOOD 1966 (811) 243, 241
WOOD 1972 (A 624) 200
WOODS 1955 (A 721) 259
WORLD HEALTH ORGANIZATION 1963 (334) 113, 111
WRAY, DEPALMA and HUBAY 1971 (155) 69, 63
WRIGHT 1968 (A 20) 13
WRIGHT 1933 (812) 245, 240
WRIGHT 1957 (A 94) 30
WYCHULIS, SPITTELL and WALLACE 1970 (A 198) 52
WYNDER and HOFFMANN 1972 (S 124) 331
WYNDER and LEMON 1958 (269) 95, 91
WYNDER LEMON and BROSS 1959 (270) 95, 91
WYNDHAM 1969 (A 414) 144
WYNN 1967 (A 278) 117
WYSONKINSKI 1971 (813) 245, 240, 479(a)
YACOUB, FAURE, MALLION and CAU 1970 (1017) 294, 289
YAMAMOTO, MURAKI and FUKUI 1966 (A 625) 200
YAMAMOTO, NAGAI and INOKI 1966 (A 760) 263
YATER, WELSH, STAPLETON and CLARK 1951 (98) 58
YOSHIKATA 1964 (A 722) 259
YOSHITOSHI, HANAOKA and MIYASHITA 1967 (A 522) 192
YOSHITOSHI, HANOKA, NAGASAKA, MIYASHITA, YAMAGUCHI, ITO, WATANABE, OSHIMA and SHINOHARA 1964 (A 523) 192
YUDKIN 1957 (A 453) 147
YUDKIN 1967 (444) 156, 153
YUDKIN 1970 (S 160) 334
YUDKIN 1973 (S 183) 335
ZAMPA, PIN and PELLEGRINI (A 293) 118
ZANNINI, CONTI and NEGRO 1963 (814) 245, 241
ZDICHYNEC and PROKS 1971 (630) 203, 201
ZDICHYRIEC 1971 (712) 221, 220
ZDRAVOOKHR ROSS FED 1971 (A 536) 193
ZEINER-HENRIKSEN 1971 (592) 183, 169
ZEJMAL 1966 (A 761) 263
ZEITLIN and TELEPNEVA 1971 (A 690) 256
ZIEGENSPECK 1963 (A 663) 227
ZUKEL, LEWIS, ENTERLINE, PAINTER, RALSTON, PAWCETT, MEREDITH and PETERSON 1959 (271) 95, 90
ZUSSMAN 1968 (156) 69, 62

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